ORGANIC
LETTERS

2013
Vol. 15, No. 8
1806–1809

Synthesis of [5]Helicenes with a Substituent Exclusively on the Interior Side of the Helix by Metal-catalyzed Cycloisomerization

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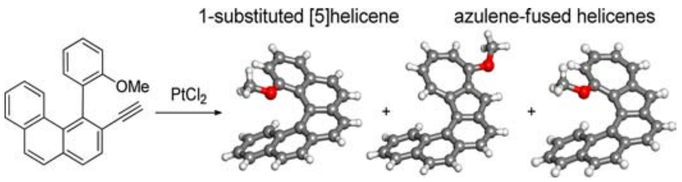
Received February 4, 2013

ABSTRACT



[5]Helicenes with a substituent exclusively oriented toward the interior curvature of the helix are synthesized by metal-catalyzed cycloisomerization. In addition, novel azulene-fused helicenes have been found through cycloisomerization studies. These [5]helicenes shows a high enough configurationally stability to allow resolution by HPLC on a chiral stationary phase.

In the past decade, helicenes have received considerable attention for potential application in chiral materials and asymmetric catalysis owing to their unique π-conjugated screw-shaped structure,[1] extraordinary chiroptical properties,[2] and self-assembly.[3] To extend the field of application of configurationally stable helicenes as functional materials and chiral catalysis, it is important to develop a facile synthetic method for the preparation of functionalized helicenes. In addition to the previously reported photochemical cyclization of stilbenes,[4] several new strategies using Diels−Alder cycloaddition,[5] olefin metathesis,[6] Friedel−Crafts cyclization,[7] and transition metal-catalyzed [2+2+2] cycloisomerization[8] of triynes or dienetriynes have been reported. In particular, the development of concise synthetic routes to configurationally stable functionalized helicenes is important in the design of optically active organic π-conjugated materials. Despite remarkable progress in the field of helicene chemistry, the development of new synthetic routes for configurationally stable [5]helicenes that allow exclusive functionalization on the interior side of the helix remains a challenge, except for photochemical cyclization.[4a] The synthesis of a series of helicenes with a substituent exclusively on the interior side of the helix is necessary to clarify the relationships between the geometric parameters and configurational stability such as the racemization energy barrier of strained or sterically hindered aromatic hydrocarbons.

We now report the synthesis of [5]helicene derivatives **1** with a functional group (R = OMe, Me, or OH) in position 1 and discuss their structures, electronic properties, and

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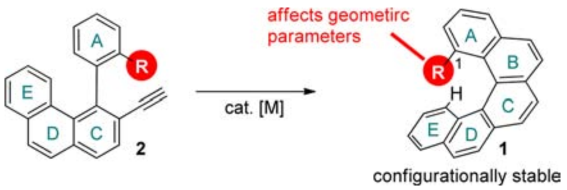
10.1021/ol400332j

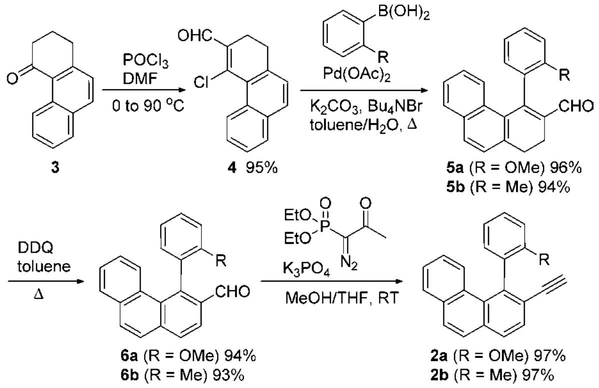
thermodynamic properties (Scheme 1). In addition, a novel synthetic reaction of azulene-fused helicenes (**7**, **8**) has been found through these studies.

Scheme 1. Synthetic Approach to 1-Functionalized [5]Helicenes



Our synthetic strategy to construct 1-functionalized [5]helicenes (**1**) was to conduct metal-catalyzed cycloisomerization by using corresponding alkynes **2** as the key precursor. The connection to the target molecules involves the closure of ring B by formation of an aromatic ring. This key reaction has already proven effective for the synthesis of a variety of phenanthrenes, polycyclic heteroarenes, and [5]helicene, as reported by Fürstner.[9] Moreover, a double cycloisomerization catalyzed by a platinum salt was recently reported by Storch and co-workers for making a 1-methoxy[6]helicene.[10]

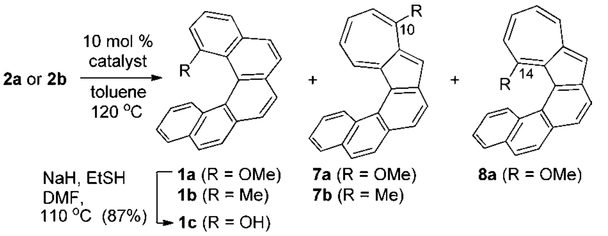
Scheme 2. Synthesis of Alkynes **2a** and **2b**



The synthesis of alkynes **2a** (R = OMe) and **2b** (R = Me), a precursor of 1-methoxy-(**1a**) and 1-methyl[5]helicene **1b**, was initiated with a Vilsmeier–Haack reaction of cyclic ketone **3** to afford β-chloroacrolein **4** in 95% yield (Scheme 2). The Suzuki-Miyaura cross-coupling of **4** with corresponding of arylboronic acids afforded **5a** and **5b** in 96% and 94% yields, respectively. The subsequent oxidative aromatization of **5** with DDQ gave **6** in high yields. Finally, the Seyferth-Gilbert homologation, using the Ohira-Bestmann reagent[11] and potassium phosphate in a mixture of methanol and THF as a solvent, afforded the corresponding alkynes **2a** and **2b** in 97 and 97% yields, respectively.

Alkyne products **2a** and **2b** were subjected to metal-catalyzed cycloisomerization for construction of [5]helicene frameworks (Table 1). When **2a** was treated with 10 mol % of AuCl in toluene at 120 °C for 24 h, 1-methoxy[5]helicene **1a** was exclusively obtained in 24% yield (entry 1). Use of $AuCl_3$ slightly increased the yield (30%, entry 2). On the other hand, the cycloisomerization of **2a** with $PtCl_2$ in toluene afforded not only the desired product **1a** (45%) but also **7a** (27%) and **8a** (5%) with an azulene moiety (entry 3). Remarkably, $PtCl_2$ in CH_3CN led to an improvement in the reaction yield of **1a** (57%, entry 4). Although the origin of this effect is not clear, a possible explanation is that the reaction selectivity is affected by $PtCl_2(CH_3CN)_2$ formed *in situ*.[12] Further, **1a** was obtained in 66% yield when an CH_3CN/toluene (1:1) mixture was employed as a solvent (entry 5). Alkyne **2b** was converted into the corresponding 1-methyl[5]helicene **1b** (44%) and **7b** (7%) using the optimized conditions for solvent mixture of CH_3CN/toluene (entry 6).

Table 1. Optimization of Metal-catalyzed Cycloisomerization[a]



entry	substrate	catalyst	time (h)	$\mathbf{1}^{b}$:$\mathbf{7}^{c}$:$\mathbf{8}^{c}$
1^d	**2a**, R = OMe	AuCl	24	24%:0%:0%
2^e	**2a**, R = OMe	$AuCl_3$	24	30%:0%:0%
3	**2a**, R = OMe	$PtCl_2$	2	45%:27%:5%
4^f	**2a**, R = OMe	$PtCl_2$	12	57%:7%:0%
5^g	**2a**, R = OMe	$PtCl_2$	7	66%:8%:2%
6^g	**2b**, R = Me	$PtCl_2$	7	44%:7%:0%

[a] The reaction was performed on a 0.16 mmol scale. [b] Isolated yields. [c] Yields were determined by ^1H NMR analysis. [d] 70% of **2a** was recovered. [e] 66% of **2a** was recovered. [f] CH_3CN was used instead of toluene. [g] CH_3CN/toluene (1:1) mixture was used instead of toluene.

The proposed mechanism for the platinum-catalyzed reaction of **2a** is illustrated in Scheme 3. Initially, activation of the triple bond occurs in catalytic processes to produce the corresponding π complex **A**. In the case of 6-*endo*-cyclization, nucleophilic addition of the carbon atom C_1–C_6 (path a) and C_1–C_2 (path b) of the phenyl moiety to the π

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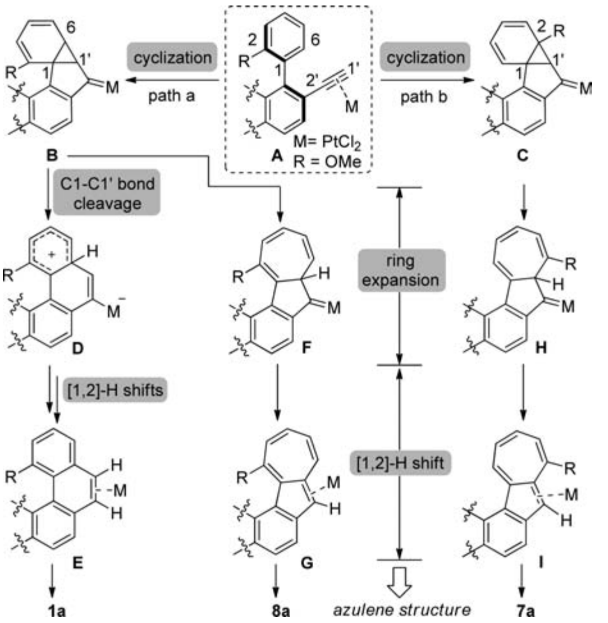
activated alkyne would give the key cyclopropyl platinum carbene intermediates **B** and **C**, respectively.[13] Opening of the cyclopropane bond $C_1-C_{1'}$ of **B** then gives Wheland-type intermediate **D**, which finally undergoes two consecutive [1,2]-H shifts to give **1a**. The intermediate **B** may also evolve to platinum carbene intermediate **F** with a 7-membered ring by 6-electron electrocyclic opening[14] of cyclopropane bond C_1-C_6. A subsequent [1,2]-H shift of intermediate **F** might afford **8a** via intermediate **G**. On the other hand, 6-electron electrocyclic opening of cyclopropane bond C_1-C_2 of **C** would give intermediate **H** with a 7-membered ring, which would finally give **7a** through a [1,2]-H shift.

Scheme 3. Proposed Reaction Mechanism for Platinum-catalyzed Cycloisomerization



To accomplish the preparation of 1-hydroxy[5]helicene **1c**, the *O*-demethylation was examined. The treatment of **1a** with sodium ethanethiolate at 110 °C afforded **1c** in 87% yield (Table 1).[15]

The structures of **1a**, **1b**, **1c**, **7a**, and **8a** were confirmed by X-ray crystal structure analysis (Figures 1 and 2).[16] The nonbonded intramolecular distance (*d*) of **1a**, **1b**, **1c** and parent [5]helicene are 2.82 Å, 3.24 Å, 3.02 Å and ca. 2.59 Å, respectively, implying that the extent of steric size is Me (A value[17] = 1.7) > HO (A value = 0.9) > MeO (A value = 0.6) > H (Figure 1). Furthermore, the X-ray analysis of **1c** revealed an intramolecular $OH\cdots\pi$ interaction, which may serve to stabilize the helical geometry.

Compound **7a** and **8a** revealed that the five (B)- and seven (A)-membered ring of the azulene unit has a highly strained nonplanar structure (Figure 2). The angles between the mean plane of the five-membered ring and the seven-membered ring of **7a** and **8a** were 8.2−8.9° and 10.4° respectively, which is larger than that (2.6°) of naphth[1,2-α]-azulene derivative.[18] The strained geometry of the azulene unit is due to the steric interaction between terminal aromatic rings and/or methoxy group. This is the first example of azulene-fused helicene derivatives with unambiguously helical geometry. Moreover, X-ray structure analysis of **7a** and **8a** revealed substantial bond-length alternation in the azulene π system (Figure S9, Supporting Information). The bond-length alternation would be induced by either highly twisted noncoplanar azulene ring, the fusion of the aromatic ring[19] to the azulene skeleton, or both.

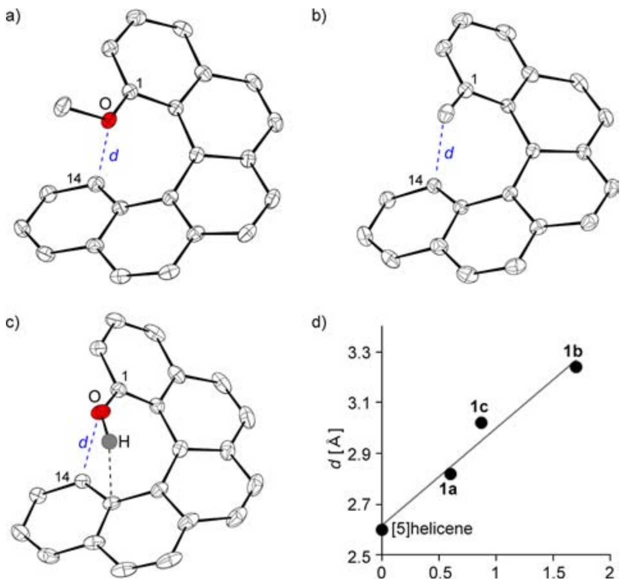


Figure 1. ORTEP representations (ellipsoids set at 50% probability) of (a) **1a**, (b) **1b**, and (c) **1c**. (d) Plots of the nonbonded intramolecular distance (d) of [5]helicene, **1a**, **1b**, and **1c** against the A value.

The separation of the enantiomers was accomplished *via* HPLC on a chiral column (Daicel Chiralpak IA, 4.6 mm ×250 mm) using a UV light detector at 254 nm.[20] The chromatogram showed successful separation of the

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[15] The use of boron tribromide afforded **1c** (29%) and benzo[ghi]perylene **9** (71%) under mild conditions (Supporting Information).

[16] CCDC 901876 (**1a**), CCDC 909678 (**1b**), CCDC 917297 (**1c**), CCDC 901883 (**7a**),and CCDC 901877 (**8a**) 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.

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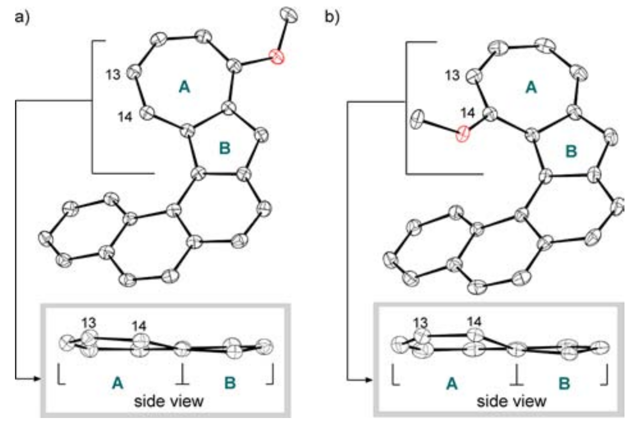

Figure 2. ORTEP representations (ellipsoids set at 50% probability) of (a) **7a** and (b) **8a**.

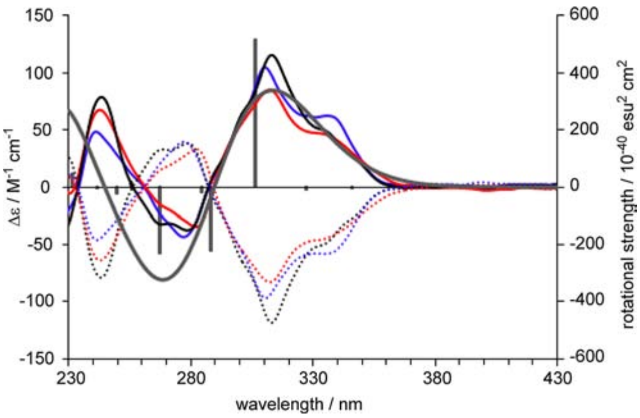

Figure 3. CD spectra of (+)-(P)-**1a** (blue solid line), (−)-(M)-**1a** (blue dashed line), (+)-(P)-**1b** (black solid line), (−)-(M)-**1b** (black dashed line), (+)-(P)-**1c** (red solid line), (−)-(M)-**1c** (red dashed line) in in $CHCl_3$ (1.0×10^{-5} M). The gray lines show the CD spectrum for (P)-**1a** calculated by the TD-DFT method at the CAM-B3LYP/6-31+G(d,p) level of theory with SMD ($CHCl_3$) solvation.

enantiomers (Table S1, Supporting Information). To assign the helicity to the resolved enantiomers, their CD spctra were measured (Figure 3). In all cases, they display mirror-image values of the (+) and (−) enantiomers within the experimental errors. Quantitative predictions with TD-DFT further validated the assigment of absolute configuration shown in Figure 3. Using the optimized molecular geometry of (P)-**1a**, rotational strengths were calculated and used to simulate the CD spectrum. Cotton effects at > 230 nm with intensity patterns similar to those experimentally observed for (P)-**1a**.

To characterize the stability of the 1-functionalized [5]helicenes **1** toward racemization, their Gibbs' free energy barriers to racemization ($\Delta G^{\ddagger}$) were measured on the basis of the time-dependent conversion rate (% ee) estimated from chiral HPLC analysis (Figure S3, Supporting Information). Although, the $\Delta G^{\ddagger}$ at 423 K of **1a** (31.7 kcal mol^{-1}) was slightly less than that of [6]helicene (36.3 kcal mol^{-1}),[21] it is clear that the presence of the 1-methoxy substituent significantly increased the racemization barrier. On the other hand, the $\Delta G^{\ddagger}$ at 473 K of **1b** (38.6 kcal mol^{-1}) was drastically increased compared to that of **1a**.[22] This could be due to a larger loss of entropy during the racemization of **1b** than **1a** and [5]helicene.[23] Thermal racemization of **1c** could not be determined because it was thermally decomposed to some unknown products.

In summary, we have successfully prepared [5]helicenes with a substituent oriented toward the interior curvature of the helix by using simple cycloisomerization. The enantiomers of 1-functionalized [5]helicenes (**1a**, **1b**, and **1c**) were separated by HPLC on a chiral column and, accordingly, the racemization barriers could be measured for the helicenes except for **1c**. Moreover, novel azulenohelicenes have been obtained through these studies. The unexpected formation of an azulene skeleton from an alkyne derivative by using a catalytic amount of $PtCl_2$ opens a new door for azulenohelicene chemistry.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Young Scientists (B) from the Japan Society for the Promotion of Science (No. 23790013). We also thank Dr. Toshihiro Murafuji at Yamaguchi University for valuable discussion. We also thank Dr. Satoru Karasawa at Kyushu University for the X-ray analysis of **1c**.

Supporting Information Available. Experimental details including synthesis and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) Azulenohelicens possess helicene-like axial chirality, but the racemization barriers are small (Figure S2, Supporting Information).

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