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Azahelicenes from the Oxidative Photocyclization of Boron Hydroxamate Complexes

Takashi Murase,* Toru Suto, and Honoka Suzuki[a]

Abstract: Aromatic hydroxamic acids (Ar–CO–NOH–Ar') were used as bidentate chelating ligands to generate the corresponding boron hydroxamate complexes, which were subsequently transformed into nitrogen-containing helicenes (azahelicenes) using an oxidative photocyclization method that is frequently used for stilbene-type (Ar–CH=CH–Ar') precursors of carbohelicenes. The nitrogen atom of the hydroxamate linker was thus directly embedded into the helicene core without using nitrogen-containing aromatic rings in the stilbene-type precursors. In a batch photoreaction, aza[4]helicenes were readily and efficiently prepared, but aza[6]helicenes underwent severe decomposition upon irradiation. Alternatively, a continuous flow photoreactor was employed to furnish an amide-type aza[6]helicene.

Helicenes, i.e., helical polyaromatic compounds consisting of *ortho*-fused aromatic rings, have attracted much attention from synthetic and materials chemists due to their unique structure and properties.[1] Several synthetic strategies toward helicenes and their homologues have been developed to date, among which oxidative photocyclizations of stilbene-type (Ar–CH=CH–Ar') compounds that afford phenanthrene frameworks represent the most commonly encountered, mostly on account of their procedural simplicity.[2] For example, [16]helicene, which is currently the longest carbohelicene reported, was successfully synthesized by multiple photocyclizations.[3] However, the same procedure cannot be applied to the synthesis of azahelicenes from imine-type precursors (Ar–CH=N–Ar'),[4] because such photocyclizations require a *Z* geometry. The corresponding *Z*-conformers of Ar–CH=N–Ar' are usually thermally unstable and exhibit a short half-life time ($\tau_{1/2}$ = ~1 s at room temperature), while the lowest (n, π^*) excited state impedes the cyclization from the (π, π^*) excited state.[5] In this context, Brønsted- or Lewis-acid-promoted photocyclizations of arylimines have been developed, albeit with poor product yields.[6] Owing to the aforementioned issues, stilbene-type precursors with nitrogen-containing aromatic rings (Ar = pyridyl or quinolyl) are usually employed. Nevertheless, the product yields are in general only moderate and lower than those for carbocyclic systems.

The problems associated with the photocyclization of imine-type precursors can be circumvented by using hydroxamic acids (R–CO–NOH–R') as bidentate chelating ligands. The corresponding boron complexes of *N*-phenylbenzohydroxamic acid possess a fixed *Z* conformation, which diminishes the influence of the lone pair of electrons on the nitrogen atom, thus enabling successful photocyclizations.[7] This method allows a direct incorporation of the nitrogen atom of the hydroxamate linker into polyaromatic molecules. However, to the best of our knowledge, the application of this concept to the synthesis of azahelicenes has not yet been reported. In this study, we demonstrate that aza[4]helicene **1** can be efficiently prepared by the oxidative photocyclization of a boron hydroxamate complex (Figure 1). In order to overcome the drawbacks of conventional batch photoreactions, which occasionally afford unstable photoproducts, we used a continuous flow technique for the synthesis of aza[6]helicene **2**.

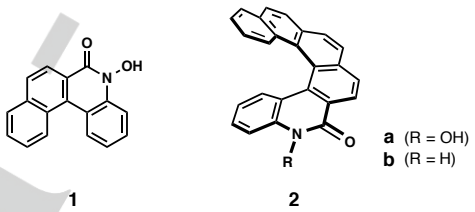
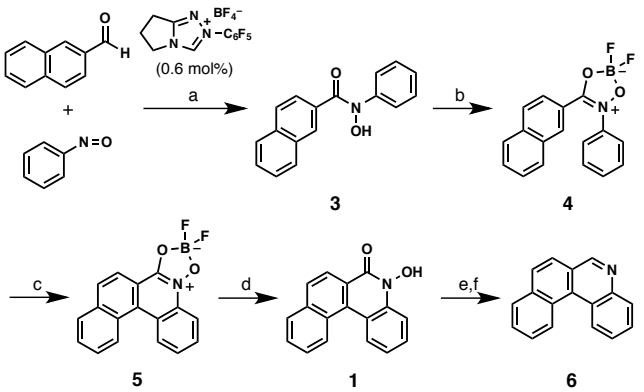


Figure 1. Aza[4]helicene **1** and aza[6]helicenes **2a,b**.

Initially, the "[2]+[1]" hydroxamic acid **3** was prepared from the *N*-heterocyclic-carbene (NHC)-catalyzed amidation[8] of 2-naphthaldehyde with nitrosobenzene in 86% yield (Scheme 1). This approach is superior to the classical *N*-acylation of hydroxylamines due to two reasons: (i) the transformation is complete within 10 min at room temperature, and (ii) nitrosobenzene is, in contrast to *N*-phenylhydroxylamine, stable and readily available.



Scheme 1. Synthesis of aza[4]helicenes **1** and **6**: a) DBU, CH_2Cl_2, 86%; b) $BF_3{\cdot}Et_2O$, Et_2O, quant; c) $h\nu$, I_2, propylene oxide, toluene; d) silica gel, $CHCl_3$, 98% over 2 steps; e) $LiAlH_4$, THF; f) *p*-toluene sulfonic acid, toluene, 81% over 2 steps.

For the oxidative photocyclization, boron hydroxamate **4**, which was obtained in quantitative yield from the treatment of hydroxamic acid **3** with $BF_3{\cdot}Et_2O$, was mixed with iodine (oxidant,

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1.1 equiv.) and propylene oxide (acid scavenger, 43 equiv.) in toluene. After 1 h of irradiation with a high-pressure Hg lamp at 30 ºC, the ^{1}H NMR signals of **4** had disappeared, and a set of new signals had emerged (Figure 2b). When we tried to isolate photocyclized product **5** from the crude mixture by column chromatography on silica gel, the BF_2 moiety was cleanly removed to furnish aza[4]helicene **1** in 98% yield (Figure 2c). However, the formation and structure of **5** was confirmed by complexation of **1** with $BF_3{\cdot}Et_2O$. A careful examination of the NMR spectrum of the photocyclization products indicated that **1** was generated in minor quantities as a byproduct (Figure 2b). Hence, although the additional treatment of **3** with BF_3 is indispensable in order to obtain the corresponding photocyclized product **1**, given that the direct photocyclization of **3** does not afford **1**, an almost quantitative transformation is still possible. Moreover, the *in situ* preparation of boron hydroxamate **4** under photoirradiation conditions was also effective and furnished **1** in excellent yield.

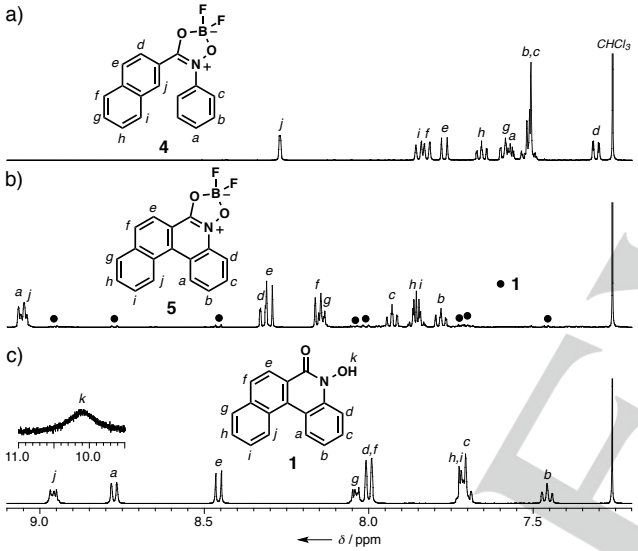
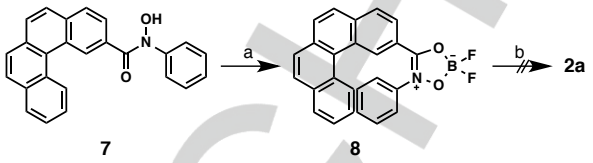


Figure 2. ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) of a) boron hydroxamate **4**, b) photocyclized product **5** before purification, and c) aza[4]helicene **1**.

Reduction of **1** with $LiAlH_4$, followed by dehydration, provided fully conjugated 5-aza[4]helicene (**6**) in 81% yield over two steps. The total yield of **6** was higher than those of previously examined non-photochemical methods using microwave irradiation in an ionic liquid,[9] or transition-metal-based catalysts.[10] Therefore, the oxidative photocyclization of boron hydroxamate **4**, followed by reduction, represents a more convenient and economic synthetic route to **6**.

Subsequently, we prepared "[4]+[1]" hydroxamic acid **7** as a precursor for aza[6]helicene **2a** (Scheme 2). As in the case of "[2]+[1]" hydroxamic acid **3**, 2-formylbenzo[*c*]phenanthrene and nitrosobenzene were coupled in the presence of the NHC catalyst, and the resulting hydroxamic acid **7** was treated with $BF_3{\cdot}THF$ in THF to afford boron hydroxamate complex **8**.[11]

Photocyclization of **8** was carried out under identical reaction conditions as for **4**. However, in contrast to **4**, the reaction was sluggish and starting material **8** remained, even after 1 h of irradiation. Upon further irradiation (4 h irradiation in total), the ^{1}H NMR signals of **8** disappeared, but only weak and broad signals were observed instead. Given that the initial purple color of the solution had turned to pale yellow, the added oxidant iodine had evidently been consumed. Therefore, we assume that the generated photocyclized product is unstable under irradiation with UV light and decomposes quickly.



Scheme 2. Attempted conversion of boron hydroxamate complex **8** into aza[6]helicene **2a**: a) $BF_3{\cdot}THF$, THF, 84%; b) *hν* (batch photoreactor), I_2, propylene oxide, toluene; (after irradiation) silica gel, $CHCl_3$.

In order to shorten the irradiation time and suppress any potential decomposition owing to overexposure to UV light, we subsequently performed the photochemical transformation of **8** using a continuous flow strategy.[12,13] For that purpose, a flow photoreactor was set up according to literature procedures:[14] fluorinated ethylene propylene tubing (FEP; outer/inner diameter = 3 mm/2 mm) was tightly wrapped around a Pyrex water-cooling jacket of a high-pressure Hg lamp (for details see the Supporting Information; Figure S1), and the irradiation area of the FEP tubing was covered with two layers of aluminum foil in order to maximize the use of UV light. Optimizing the reaction conditions ([**8**] = 0.80 mM, flow rate = 0.37 mL/min, atmospheric conditions) furnished aza[6]helicene **2b**, containing an amide moiety, in 16% yield. We discovered that the N–O bond of **8** is easily broken, which leads to substantial degradation under irradiation conditions (Figure 3a).

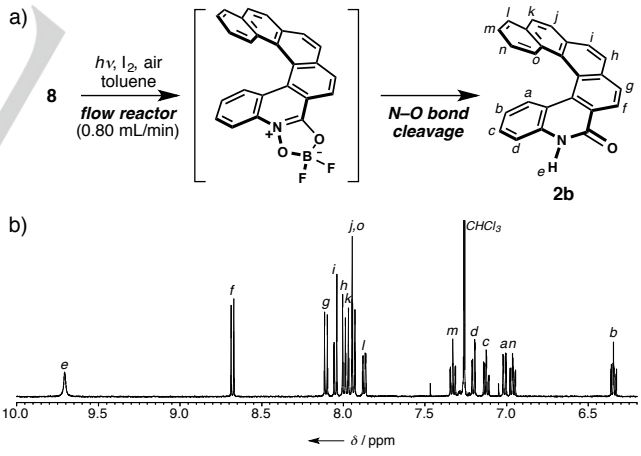


Figure 3. a) Photochemical conversion of boron hydroxamate complex **8** into aza[6]helicene **2b** in a continuous-flow reactor. b) ^{1}H NMR spectrum of **2b** (500 MHz, $CDCl_3$, 298 K).

The structure of **2b** was determined by 1D and 2D NMR spectroscopy and mass spectrometry. In the 1D ^{1}H NMR spectrum, the terminal aromatic proton (H_b) of the amide side was significantly upfield shifted (δ = 6.35 ppm), due to the close proximity of the benzene ring at the opposite helical end (Figure 3b). In fact, it was difficult to distinguish between aza[6]helicenes **2a** and **2b** in the NMR analysis, as both compounds should exhibit similar NMR spectra on account of the broad signals that should be expected from the hydroxamic acid and amide

protons. Nevertheless, conclusive evidence for the formation of **2b** was obtained from the ESI-MS analysis, which showed prominent ion peaks for [**2b**+Na]$^+$. Moreover, in contrast to the case of **1**, the treatment of **2b** with BF_3·THF did not erase the broad signal of H_e in the ^{1}H NMR spectrum, indicating that the corresponding boron complex was not generated, and that the hydroxamic acid moiety was thus no longer present in the structure.

In summary, we successfully accomplished the synthesis of azahelicenes by the oxidative photocyclization of boron hydroxamate complexes. Boron hydroxamate complexes are accordingly able to compensate for the drawbacks typically associated with the photocyclization of imines. Boron hydroxamate complex **4**, with a "[2]+[1]" sequence, readily cyclized to quantitatively afford aza[4]helicene **1**. The photocyclization of boron hydroxamate complex **8**, with a "[4]+[1]" sequence, was conducted in a continuous-flow reactor in order to minimize decomposition, which allowed the isolation and characterization of amide-type aza[6]helicene **2b**. The thus obtained azahelicenes may subsequently find applications as chiral ligands,[15] and asymmetric organocatalysts.[16] Studies on hydroxamic acid **1** as a bidentate helicene-type ligand are currently in progress in our laboratory.

Experimental Section

Experimental and characterization details can be found in the Supporting Information.

Acknowledgements

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Keywords: continuous flow • helicenes • helical structures • hydroxamic acids • photocyclization

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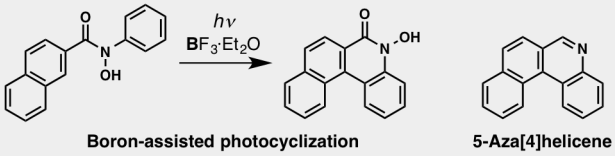

Takashi Murase, Toru Suto, and Honoka Suzuki*

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Azahelicenes from the Oxidative Photocyclization of Boron Hydroxamate Complexes

Azahelicenes: Aromatic hydroxamic acids were converted into azahelicenes by complexation with boron trifluoride etherate, followed by oxidative photocyclization. The nitrogen atom of the hydroxamate linker was thus directly embedded into the helicene core, which led to the facile formation of 5-aza[4]helicene in the most efficient manner reported so far.