

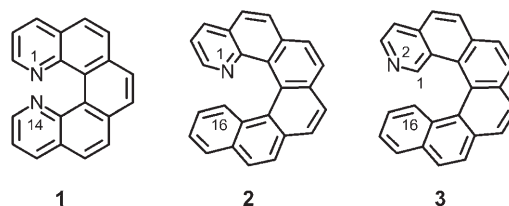
A Straightforward Route to Helically Chiral N-Heteroaromatic Compounds: Practical Synthesis of Racemic 1,14-Diaza[5]helicene and Optically Pure 1- and 2-Aza[6]helicenes**

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In memory of Otto Exner

Helicenes have attracted attention as unique inherently chiral three-dimensional aromatic compounds for several decades. Despite significant recent progress in the synthesis and applications of carbohelicenes and thiaheterohelicenes,^[1] the potential of the aza analogues with a pyridine unit (pyridohelicenes) have not been explored.^[2,3] There are only scattered examples of the preparation of pyridohelicenes,^[4] but with no general synthetic methodology, since the photochemical approach can fail with pyridohelicenes^[4b,c,e] while non-photochemical alternatives can be difficult to adapt to the synthesis of N-heteroaromatic compounds. The properties and chemical behavior of pyridohelicenes are practically unknown apart from their basicities^[4e,g] and the self-assembly^[5] of certain derivatives. Nevertheless, promising applications of pyridohelicenes in various branches of chemistry and material science might be envisaged and, therefore, further research in the field is required.

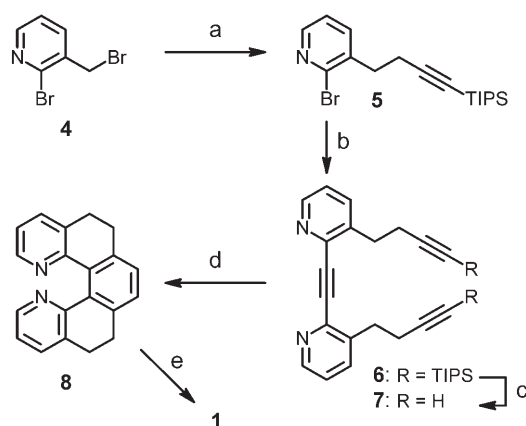
Recently, we observed remarkably high proton affinities of pyridohelicene derivatives, as measured by mass spectrometric techniques.^[6] In the gas phase, helically chiral 1-aza[6]helicene (**2**, Scheme 1), for example, exhibits a comparable proton affinity (1000 kJ mol⁻¹) to 4-(dimethylamino)-pyridine (DMAP, 997 kJ mol⁻¹). Herein, we report the practical syntheses of 1,14-diaza[5]helicene (**1**),^[7] 1-aza[6]helicene (**2**),^[8] and 2-aza[6]helicene (**3**).^[9] Moreover, we have



Scheme 1.

succeeded in resolving racemates of **2** and **3** into their enantiomers, assigning their absolute configuration, determining the energy barriers to racemization, and obtaining X-ray structures of their corresponding silver complexes.

The strategy for the preparation of **1–3** relies on a [2+2+2] cyclotrimerization of an aromatic triyne in the presence of a Co^I catalyst to build the helical scaffold. We have already proven that such a methodology is robust and reliable for the preparation of helicenes and their analogues.^[10] Thus, the straightforward synthesis of **1** started from the readily accessible bromopyridine **4**,^[11] which was treated with lithiated 1-(triisopropylsilyl)-1-propyne to yield **5** which contained an attached alkyne side arm (Scheme 2). Sonoga-



Scheme 2. Synthesis of 1,14-diaza[5]helicene (**1**): a) TIPS-C≡CCH₃ (1.1 equiv), *n*BuLi (1.1 equiv), THF, -78 °C to RT, 30 min, 81%; b) HC≡CH (gaseous), [Pd(PPh₃)₄] (5 mol%), CuI (15 mol%), piperidine, 80 °C, 30 min, 86%; c) *n*Bu₄NF (2.5 equiv), THF, RT, 1 h, 77%; d) [CpCo(CO)₂] (20 mol%), PPh₃ (40 mol%), decane, halogen lamp, 140 °C, 1 h, 60%; e) MnO₂ (30 equiv), toluene, microwave oven, 150 °C, 20 min, 41%. TIPS = triisopropylsilyl, Cp = C₅H₅.

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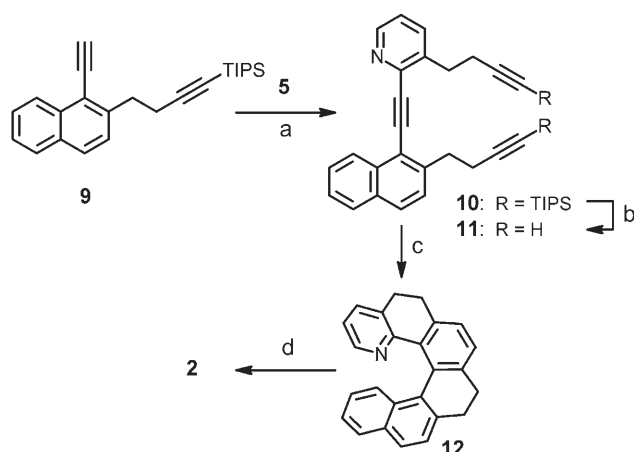
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shira coupling with gaseous acetylene under Pd^0/Cu^I catalysis gave pyridotriyne **6**, which was desilylated with tetrabutylammonium fluoride to provide the unprotected pyridotriyne **7**. The key $[\text{CpCo}(\text{CO})_2]$ -catalyzed cyclotrimerization led smoothly to tetrahydrodiazahelicene **8**. However, its conversion into the fully aromatic system **1** represented the most difficult step of the whole synthesis. The oxidants routinely used either failed or afforded mixtures with only trace amounts of the desired product. We finally found that the use of MnO_2 in combination with microwave irradiation was a superior aromatizing reagent, which afforded pyridohelicene **1** in reasonable yield.

The synthesis of the higher homologue **2** (Scheme 3) followed the same route described above. To assemble the

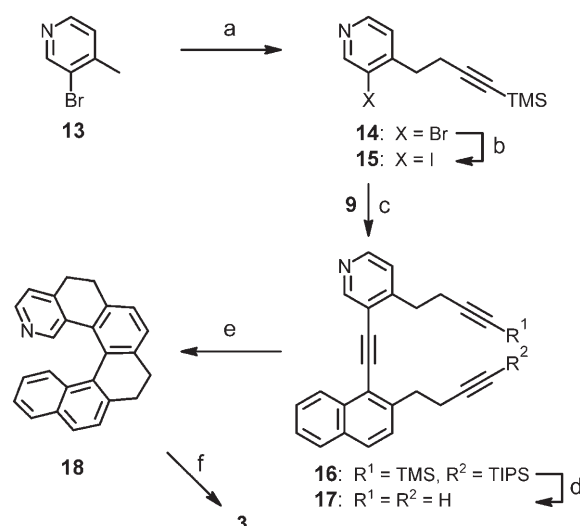


Scheme 3. Synthesis of 1-aza[6]helicene (**2**): a) $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol%), CuI (10 mol%), diisopropylamine/toluene, RT, 1.3 h, 90%; b) $n\text{Bu}_4\text{NF}$ (2.5 equiv), THF, RT, 30 h, 92%; c) $[\text{CpCo}(\text{CO})_2]$ (20 mol%), PPh_3 (40 mol%), decane, halogen lamp, 140°C , 1 h, 82%; d) MnO_2 (30 equiv), toluene, microwave oven, 150°C , 1.3 h, 65%.

pyridyl-naphthyl triyne scaffold, pyridoalkyne **5** was smoothly coupled under Pd^0/Cu^I catalysis with the known naphthyl-triynyl **9**^[10c] to give **10**. After desilylation, pyridotriyne **11** underwent a Co^I -catalyzed cyclotrimerization to give tetrahydroazahelicene **12**. Similar to the previous case, only microwave-assisted oxidation in the presence of MnO_2 led to fully aromatic pyridohelicene **2**. The structures of **12** and **2** were confirmed by X-ray analysis.^[12]

By taking advantage of the modularity of the synthetic approach, the regioisomer **3** could be prepared in the same way as **2**, except that a pyridoalkyne building block needed to be synthesized (Scheme 4). The structure of pyridohelicene **3** was confirmed by X-ray analysis.^[12]

As far as the resolution of racemic **2** and **3** was concerned, we benefited greatly from the presence of a basic nitrogen atom in the pyridohelicene scaffolds. After some experimentation with various optically pure acids as resolving agents, we found that the use of (+)-*O,O'*-dibenzoyl-D-tartaric acid in a large excess led to the formation of a yellow crystalline diastereomeric complex with 1-aza[6]helicene (**2**; ca. 2:1 stoichiometry). A basified sample of the complex showed it to have an enantioselectivity of 75% *ee* in favor of (+)-**2**,



Scheme 4. Synthesis of 2-aza[6]helicene (**3**): a) LDA (1.0 equiv), THF, 50°C , 45 min, then $\text{TMS-C}\equiv\text{CCH}_2\text{Br}$ (1.1 equiv), 0°C to RT, 3 h, 93%; b) $n\text{BuLi}$ (1.1 equiv), diethyl ether, -78°C , 30 min, then iodine (1.5 equiv), -78°C to RT, 1.5 h, 82%; c) $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol%), CuI (10 mol%), diisopropylamine, RT, 40 min, 91%; d) $n\text{Bu}_4\text{NF}$ (2.5 equiv), THF, RT, 1 h, 84%; e) $[\text{CpCo}(\text{CO})_2]$ (20 mol%), PPh_3 (40 mol%), decane, halogen lamp, 140°C , 1 h, 89%; f) MnO_2 (30 equiv), toluene, microwave oven, 130°C , 30 min, 53%. LDA = lithium diisopropylamide, TMS = trimethylsilyl.

according to HPLC analysis on a Chiralcel OD-H column. Trituration of the solid complex in diethyl ether at reflux, subsequent formation of the free base with sodium hydroxide, and its recrystallization led to optically pure pyridohelicene (+)-**2** ($[\alpha]_D = +3615 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ in CH_2Cl_2 , > 99% *ee*). The optical antipode (−)-**2** ($[\alpha]_D = -3631 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ in CH_2Cl_2 , > 99% *ee*) was separated from the mother liquor by using (−)-*O,O'*-dibenzoyl-L-tartaric acid in the above-described procedure.

Racemic pyridohelicene **3** was easily resolved by HPLC on a Chiralcel OD-H column (heptane/isopropanol 3:1). Separation and crystallization led to the two optically pure enantiomers (+)-**3** ($[\alpha]_D = +3825 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ in CH_2Cl_2 , > 99% *ee*) and (−)-**3** ($[\alpha]_D = -3840 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ in CH_2Cl_2 , > 99% *ee*).

To assign the helicity to the resolved enantiomers, their CD spectra were measured and correlated with the spectrum of (+)-(*P*)-[6]helicene (**19**),^[13] whose absolute configuration is known.^[14] We found a notable agreement between the CD characteristics of (+)-(*P*)-**19** and those of (+)-**2** and (+)-**3**, so we could ascribe unambiguously *P* helicity to the dextrorotatory enantiomers and *M* helicity to the laevorotatory enantiomers (Figure 1).

It is known that helicenes can be racemized.^[1b] In the case of [6]helicene (**19**), such a conformational process is characterized by a free energy barrier of $154.5 \text{ kJ mol}^{-1}$ at 188°C .^[15] However, the corresponding data for pyridohelicenes had not previously been determined. Thus, we attempted the thermal racemization of single enantiomers of **2** as well as of **3** while monitoring the *ee* values by HPLC analysis on a Chiralcel OD-H column. From these kinetic measurements we calculated the barriers to racemization (ΔG) as $(134.7 \pm$

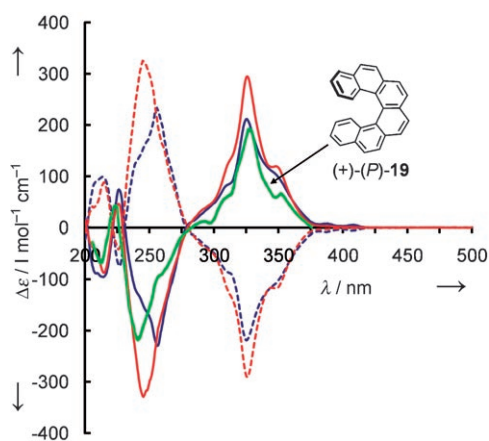


Figure 1. CD spectra of (–)-(M)-1-aza[6]helicene (**2**; blue dashed line), (+)-(P)-1-aza[6]helicene (**2**; blue solid line), (–)-(M)-2-aza[6]helicene (**3**; red dashed line), (+)-(P)-2-aza[6]helicene (**3**; red solid line) in acetonitrile (4.70×10^{-4} M) as well as the spectrum of (+)-(P)-[6]helicene (**19**; green line) in methanol as a reference (1.65×10^{-5} M).^[13]

0.1) kJ mol^{−1} for **2** (at 140 °C) and (147.7 ± 0.3) kJ mol^{−1} for **3** (at 188 °C). It is thus evident that 2-aza[6]helicene (**3**) behaves similarly to parent [6]helicene (**19**), but that 1-aza[6]helicene (**2**) behaves differently. The significantly lower energy barrier to racemization of **2** reflects the smaller steric repulsion between the lone pair of electrons on N(1) and the H-C(16) proton in **2** than that between the H-C(1) and H-C(16) protons in **3**, which is expected to occur on formation of a “C_s” transition state.^[16]

Compounds **1–3** comprising pyridine unit(s) might serve as N ligands for transition metals. Indeed, mixing silver(I) triflate separately with racemic **2** and **3** afforded the corresponding 1:2 Ag^I pyridohelicene complexes, and crystals suitable for X-ray analysis were obtained (Figure 2). Both Ag^I complexes (*P*,P**)-**20** and (*P*,P**)-**21** exhibit a T-shaped structure in which two homochiral pyridohelicene units are coordinated. Notably, the silver atom in **20** is embedded within the π-electron system so that the distances between the centroids of the C(6a)–C(16b) and C(6a′)–C(16b′) bonds (2.901(2) and 2.916(2) Å) fall well below the sum of the van

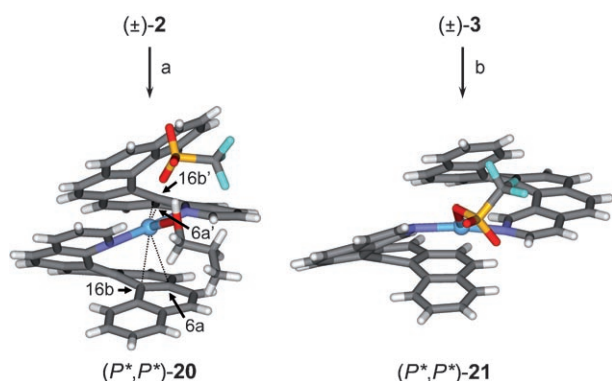


Figure 2. X-ray structures of (*P*,P**)-**20** [$[\text{Ag}\{(\text{P}^*)\text{-2}\}_2(\text{CH}_3\text{CH}_2\text{CH}_2\text{OH})\text{]}[\text{CF}_3\text{SO}_3]$] and (*P*,P**)-**21** [$[\text{Ag}\{(\text{P}^*)\text{-3}\}_2[\text{CF}_3\text{SO}_3]$]: a) AgOTf (0.6 equiv), toluene, RT, crystallized from heptane/propan-1-ol; b) AgOTf (0.6 equiv), toluene, RT, crystallized from toluene. OTf = CF₃SO₃.

der Waals radii ($\Sigma_{\text{Ag,C}} = 3.42$ Å). Hence, the coordination environment around the silver atom is best described as a trigonal bipyramid, in which each 1-aza[6]helicene binds as an N,C-bidentate ligand, with the nitrogen atom and C=C bond occupying axial and equatorial positions, respectively. Consequently, selected azahelicenes might join the family of novel chiral olefin-type ligands, which have attracted considerable attention in the asymmetric catalysis community.^[17]

In summary, we have developed a new practical synthesis of penta- and hexacyclic pyridohelicenes, which so far have been rather neglected. Moreover, 1- and 2-aza[6]helicenes have been obtained for the first time in an optically pure form and their helicity have been assigned. We have confirmed their sufficient configurational stability as well as their ability to form transition-metal complexes. This finding makes chiral pyridohelicenes attractive candidates for further application in various areas of chemistry such as, for example, (organo)-catalysis, coordination chemistry, and molecular recognition.

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