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Synthesis of Functionalized Dioxa-aza[7]helicenes Using Palladium Catalyzed Arylations

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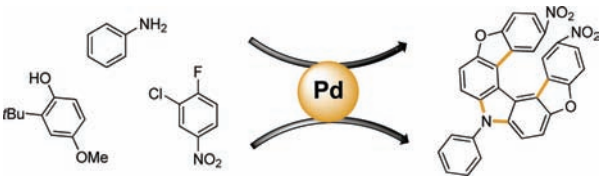
ABSTRACT



Despite the recent reports on transition-metal catalyzed cycloisomerization strategies toward helicenes, the amount of palladium catalyzed routes remains rather scarce. Within this letter the successful preparation and characterization of novel dioxa-aza[7]helicenes using palladium mediated coupling reactions is presented.

During the past decades, helicenes gained a considerable amount of attention, and not only by synthetic chemists. Their unique helical shaped backbone, which is formed by a successive annulation of (hetero) aromatic rings, has led to an impressive number of diverse applications, mostly based on the inherently chiral conformation.[1] Remarkable examples of this applicability include chiral catalysis,[2] self-assembly,[3] and biomolecular recognition.[4]

The recently increased interest in these areas is most likely caused by the inspiring discoveries made during the pursuit toward new synthetic approaches that avoid photochemical cyclizations,[5] a field now dominated by the cycloisomerization-based methods first reported by Starý and Stará in 1998.[6] However, despite this sudden growth in transition-metal based procedures, synthetic routes using palladium catalyzed coupling reactions as a crucial step in the formation of a helicene are rare, probably due to the challenging preparation of an appropriate precursor. Notable examples thus far include a Buchwald–Hartwig arylation[7] and a double C–H activation[8] (Scheme 1). However, both approaches are suffering from certain drawbacks. First, compounds like **1** are not readily

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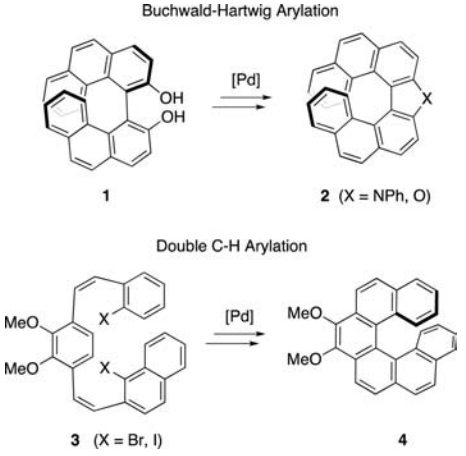
accessible, hampering further derivatization; second, the double C−H arylations experience low yields caused by the increasing steric hindrance and dehalogenation. These findings prompted us to investigate other, more efficient and general routes using these palladium-mediated methods.

Scheme 1. Examples of Palladium Catalyzed Routes towards Helicenes

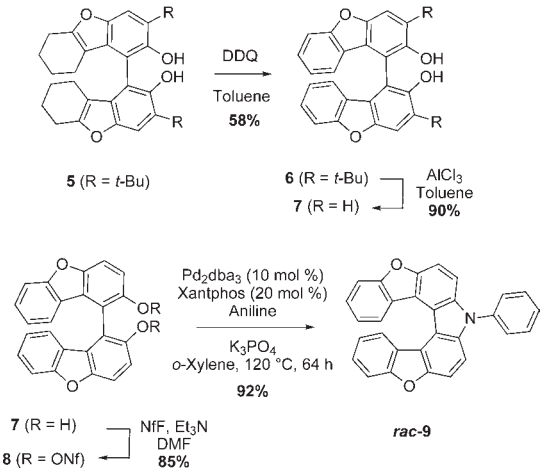


In addition, we will be focusing on the implementation of oxygen-based heterocycles (i.e., dibenzofuran), as this could open an opportunity to study the electro-optical properties of the otherwise uncommon oxa-helicenes.

The classic approach toward dimeric structures like bisphenanthrol **1** depends on the oxidative coupling of an appropriate phenolic unit. Earlier we reported such a strategy to yield a novel scaffold; H_8-1,1′-bis(dibenzofuran-2-ol) or H_8-BIFOL **5**,[9] an ideal candidate for exploring further reaction conditions as it can be prepared in large amounts. Initial optimization studies revealed that oxidation of the saturated rings prior to the final N-arylation step was essential to ensure acceptable yields of the helicene. Several oxidation agents were screened. However, only dichlorodicyanobenzoquinone (DDQ) could convert **5** into its aromatized analogue **6**. Removal of the *tert*-butyl groups of **6** was achieved using conventional conditions, allowing an effortless substitution of diphenol **7** with nonafluorobutanesulfonyl fluoride (NfF), providing bis-nonaflate **8** as a benchtop stable compound (Scheme 2). Due to the higher racemization barrier of an aza-helicene compared with the corresponding oxa-helicene,[7,10] a double N-arylation was selected to bridge the two dibenzofuran units, creating the novel dioxa-aza[7]helicene **9** in good yields.

Crystals of *rac*-**9** suitable for X-ray analysis were obtained by vapor diffusion, from a chloroform−pentane system. The racemic compound crystallizes in the centrosymmetric

Scheme 2. Synthesis of Dioxa-aza[7]helicene **9**



triclinic space group $P\bar{1}$, with one molecule in the asymmetric unit, as depicted in Figure 1. The distortion of the molecular structure (53.2°), defined by the sum of the five dihedral angles, namely, C16−C12−C9−C3, C12−C9−C3−C4, C9−C3−C4−C17, C3−C4−C17−C21, C4−C17−C21−C24, is substantially smaller than the value reported by Nozaki et al. (83.6°) for the phenanthrene analogue **2** (X = N-Ph)[7] due to the presence of the furan rings (smaller overlap between the outer rings leads to a reduced steric repulsion). Viewed down the *a*-axis, the molecules form columns of alternating opposite enantiomers (see Supporting Information), held together by different kinds of weak interactions. $\pi-\pi$ stacking occurring between pyrrole rings and the benzene rings (C2−C9) is followed by $\pi-\pi$ stacking between the former pyrrole rings and benzene rings (C4−C20), with centroid−centroid distances of 3.705(1) and 3.618(1) Å respectively. C−H$\cdots\pi$ interactions involving the nonfused benzene ring and the furan rings (C29−H29$\cdots$*Cg*1; *Cg*1 = centroid of the O10 furan ring, and C33−H33$\cdots$*Cg*2, *Cg*2 = centroid of the O23 furan ring; C29$\cdots$*Cg*1 = 3.440(2) Å and C33$\cdots$*Cg*2 = 3.331(2) Å) combined with C−H$\cdots$O hydrogen bonds (C33−H33$\cdots$O23 with C$\cdots$O = 3.370(2) Å) further support the columnar formation. A similar packing feature was observed for thiohelicenes.[11] Additional C−H$\cdots$O interactions between isochiral molecules (C7−H7$\cdots$O23 with a C$\cdots$O distance of 3.379(2) Å) interlink the columns, resulting in a 3-D assembly.

However, in order to be applicable in new useful materials, **9** has to be further functionalized. Considering the electron-rich carbazole segment, it would be advantageous to implement electron-deficient functionalities on the outer rings, which should improve the electro-optical properties significantly.[12] For this purpose, a series of substituted dibenzofuran moieties was prepared starting from the

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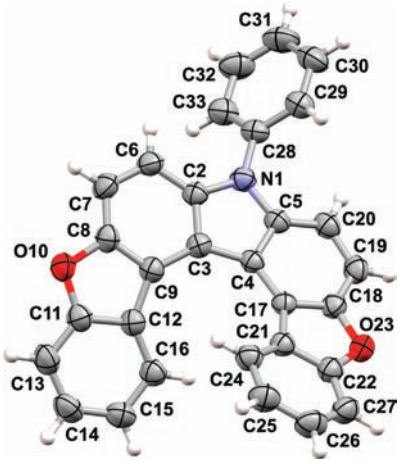
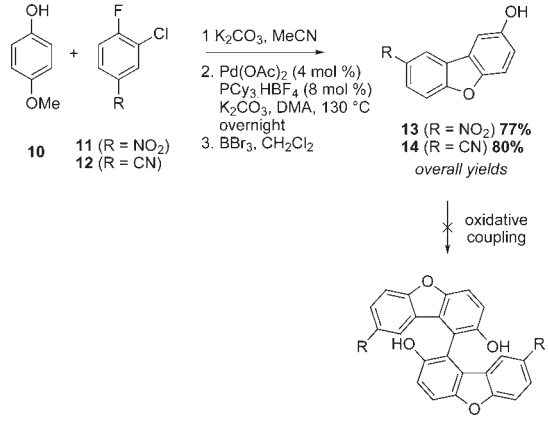


Figure 1. Molecular structure of **9**. Displacement ellipsoids are drawn at the 50% probability level.

commercially available compounds **10**–**12** (Scheme 3). A nucleophilic aromatic substitution followed by a palladium catalyzed arylation provided the appropriate phenolic dibenzofuran units **13** and **14** after quantitative deprotection using BBr_3. Unfortunately, none of the conditions that were investigated for the oxidative dimerization of these building blocks was able to provide the desired coupled products (Scheme 3). A plausible reason for the lack of reactivity is the increased oxidation potential due to the presence of these electron-withdrawing groups.

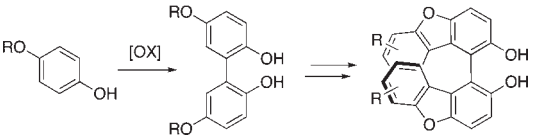
Scheme 3. Synthesis and Oxidative Coupling of Substituted Dibenzofuran Moieties



An obvious, yet unprecedented way to avoid this kind of problem is to reverse the approach, that is by starting with an oxidative coupling of less complex, electron-rich segments, followed by an extension to the substituted dibenzofuran moieties (Scheme 4).

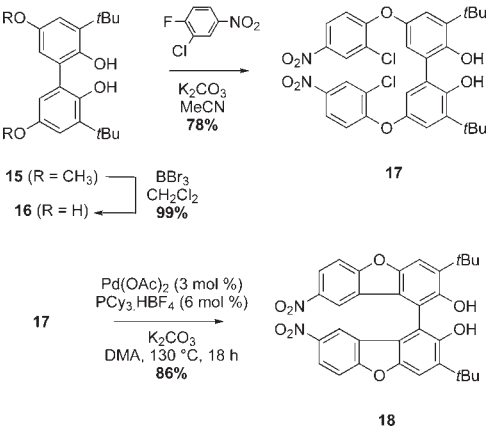
The known compound, bis-*tert*-butylated hydroxyanisole (bis-BHA) **15**, was selected as a scaffold to construct

Scheme 4. Alternative Approach to Bis-dibenzofuranol Derivatives



the dibenzofuran units for several reasons. First, it is readily prepared on a large scale by oxidative coupling of BHA, a cheap, commercially available reagent. Second, the bulky *tert*-butyl substituents control both the nucleophilic aromatic substitution and the C–H arylation step toward the desired regioisomers. As expected, demethylation using BBr_3 afforded the bis-hydroquinone **16** in quantitative yields (Scheme 5). Although two of the hydroxyl groups are obstructed by the *tert*-butyl substituents, careful regulation of the temperature seemed crucial to prevent the formation of oversubstituted products, allowing yields up to 78% of the targeted disubstituted compound **17**.

Scheme 5. Synthesis of Substituted Bis-dibenzofuran **18**



Investigation of the palladium catalyzed C–H arylation revealed that the use of $Pd(OAc)_2$ in combination with PCy_3 (added as the air-stable tetrafluoroborate salt) were optimal conditions for the ring closure to **18**, which is in good agreement with earlier reports concerning the palladium mediated intramolecular arylation of biaryl chlorides by Fagnou et al.[13] As assumed, the structural flexibility of the biaryl system did not hamper the double C–H activation, resulting in a near-quantitative conversion without any trace of dehalogenation or partially reacted material (Scheme 5).

Due to the analogy with the biaryl system **6** prepared earlier, similar conditions could be employed for the synthesis of helicene **21**. Again, good yields were found for the

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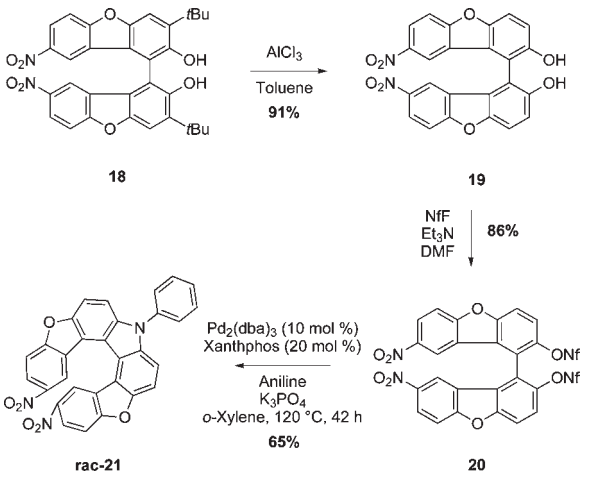
Scheme 6. Synthesis of 2,13-Dinitrodioxa-aza[7]helicene **21**



dealkylation to **19** and double Buchwald–Hartwig amination starting from the corresponding dinonaflate **20** (Scheme 6). 2,13-Dinitro-dioxa-aza[7]helicene **21** was obtained as a bright yellow solid with no visible fluorescence due to the quenching effect of the nitro substituents, which can be a useful advantage during second-order NLO measurements.

In summary we have discovered efficient routes toward a novel helical scaffold, dioxa-aza[7]helicene. Both approaches made use of palladium catalyzed arylations to construct the crucial bonds in the helicene backbone. Although the oxidative coupling of the dibenzofuranol unit could not be used for substituted derivatives, an alternative route was found by reversing this first strategy. We believe that these approaches will form a constructive addition to the field of helicene synthesis. Further functionalization and resolution of the new scaffold is currently ongoing and will be reported in due course.

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Supporting Information Available. Additional X-ray data, copies of ^{1}H and ^{13}C NMR spectra and UV spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.