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A Scalable and Expedient Route to 1-Aza[6]helicene Derivatives and Its Subsequent Application to a Chiral-Relay Asymmetric Strategy

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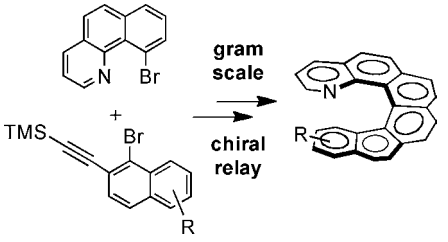
ABSTRACT



A rapid route to diversely functionalized 1-aza[6]helicenes has been achieved via the development of a copper-mediated cross-coupling reaction, followed by $PtCl_4$-catalyzed cycloisomerization. Not only does this method allow access to these functionally important molecules on gram scale, but this strategy is also suitable for relaying the axial chirality of a key intermediate to the helicity of the product.

Interest in the inherently chiral aromatics known as the helicenes continues to expand due to their fascinating helical, and therefore chiral, topology coupled with their fully conjugated aromatic structure.[1] These chiral aromatics promise to have wide-ranging impact, with preliminary studies already reported in the fields of catalysis,[2−7] nonlinear optics,[8] electrooptical switches,[9] and molecular recognition,[10−13] among others. Azahelicenes (such as **4**) have been a particularly exciting target class of helicenes recently for chemical synthesis,[1−3,14] exhibiting fascinating coordination chemistry,[13−16] self-assembly potential,[17] and interesting photophysics.[18] We

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have recently demonstrated the high potential of this class in materials science, using enantiopure dopant quantities of 1-aza[6]helicene (**4**) to induce circularly polarized (CP) electroluminescence from an achiral light-emitting polymer[19] and fabricating organic phototransistors based on **4** that can reversibly detect CP light.[20] Furthermore, there has been much interest in exploiting the chiral scaffold of azahelicenes in asymmetric organocatalysis (Figure 1). Takenaka and co-workers have reported 1-azahelicene derivatives **1** and **2** as helical organocatalysts[2a−d] for enantioselective ring-opening of *meso*-epoxides, the addition of dihydroindoles to nitroalkenes, and the propargylation of aldehydes with allenyltrichlorosilane. Starý, Stará, and co-workers also used 1-aza-(**4**) and 2-aza[6]helicene (**5**) as organocatalysts in the asymmetric acyl-transfer reactions of *rac*-1-phenylethanol.[2e] Similarly, kinetic resolution chemistry has been reported by Carbery and co-workers using a helicenoidal DMAP analogue **3**, with good to excellent levels of selectivity ($S \leq 116$).[3]

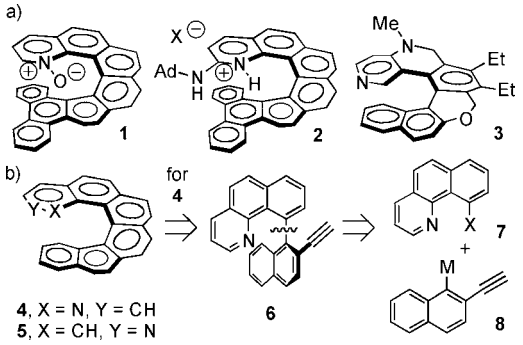


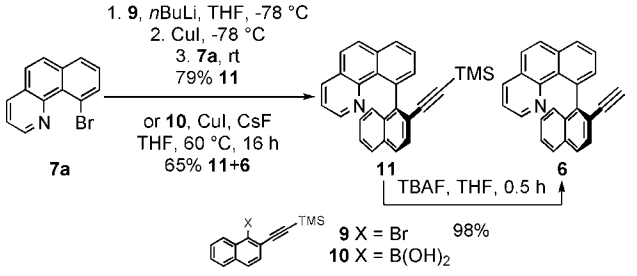
Figure 1. (a) Azahelicene or helicenoid chiral organocatalysts; (b) retrosynthetic analysis of target helicene **4**.

Despite these exciting preliminary applications, one of the key limitations for azahelicene study is access to significant quantities of material. Only limited reports have concerned the synthesis of helicene enantiomers on a >1 g scale,[21] and the current routes reported toward 1-aza[6]helicenes (**4**) have several drawbacks. For example, the Takenaka route[2a,b] involves seven linear steps to assemble three fragments, all of which are noncommercially available, and it uses significant amounts of hexamethylditin to mediate two aryl−aryl bond formation steps. Alternatively, the route developed by Starý, Stará, and co-workers[14] comprises eight linear steps starting from two noncommercial fragments and requires 30 equiv of MnO_2 in a final oxidation step. In both cases, the enantiopure products were obtained by semipreparative chiral HPLC or crystallization of diastereomeric salts.

To enable a more rapid synthesis of 1-aza[6]helicene (**4**), we envisaged disconnecting to key biaryl species **6** via a cycloisomerization reaction (Figure 1b). Cycloisomerization has been shown to be an applicable synthetic strategy to prepare carbohelicenes,[22] although very limited success has been obtained when using this chemistry on systems bearing π-deficient pyridine moieties.[23] Indeed, in general, only electron-rich systems have been reported as suitable substrates,[24] thus allowing significant scope for improvement. Further disconnection of the aryl−aryl bond in **6** would lead to readily available benzo[*h*]quinoline derivatives **7** and functionalized naphthalenes **8**. While we suspected the formation of such a hindered biaryl bond in **6** would be challenging, the likely high barrier to rotation about the aryl−aryl bond was seen as an opportunity to isolate axial stereoisomers of **6**, the stereochemistry of which could potentially be selectively relayed to the helical product.

We commenced our attempts to construct the crucial biaryl bond in **6** by using either C−H arylation chemistry[25] or conventional metal-catalyzed cross-coupling methodology; however, we found that the vast majority of processes attempted failed to deliver the hindered biaryl product. With 10-bromobenzo[*h*]quinoline **7a**,[26] alkyne **9**,[27] and boronic acid **10** in hand, we instead decided to investigate the use of copper salts.[28] With a stoichiometric amount of CuI, the cross coupling of bromide **7a** with boronic acid **10** in THF and in the presence of CsF afforded a mixture of **11** and **6** in moderate yield, whereby the TMS group had been partially cleaved (Scheme 1). Following optimization, we found that the cuprate of **9**, formed in situ via lithium−bromide exchange and transmetalation with CuI, reacted with **7a** to give **11** in high yield (79%).

Scheme 1. Synthesis of Key Intermediate **6**



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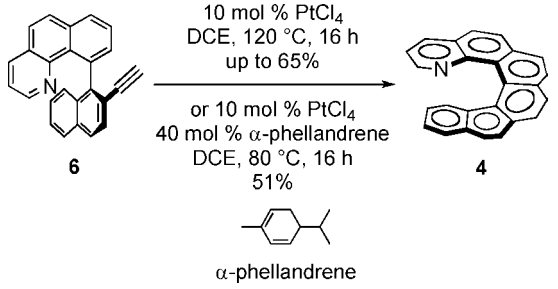
With key biaryl **11** in hand, the cycloisomerization of deprotected alkyne **6** was investigated. As suspected, this was highly challenging, with well-established π-Lewis acids, such as $PtCl_2$, $InCl_3$, and $GaCl_3$ in addition to other gold and ruthenium complexes, failing to give any conversion. This was shown to be due to the presence of the pyridine functionality (see the Supporting Information). Since sporadic reports have emerged demonstrating $PtCl_4$ to be more effective than $PtCl_2$ in similar reactions,[29] we examined this catalyst. Storch et al. reported the successful cycloisomerization of a single related substrate,[23] using 0.05 equiv of $PtCl_4$ and 0.05 equiv of $InCl_3$ at 90 °C in toluene, although this chemistry had poor substrate scope. In our hands, even with 0.5 equiv of each Lewis acid, only traces of product were obtained when using substrate **6**. Raising the reaction temperature to 120 °C in DCE, however, gave a much improved conversion. At this increased temperature we found $InCl_3$ to be unnecessary, and we were able to lower the catalyst loading of $PtCl_4$. Indeed, when the reaction was carried out in the presence of 10 mol % of $PtCl_4$ at 120 °C, the helicene product **4** was obtained in up to 65% yield (Scheme 2). We found this procedure could be further telescoped by employing substrate **11** in the cycloisomerization reaction directly. The TMS group was cleaved in situ and product **4** isolated in comparable yield.

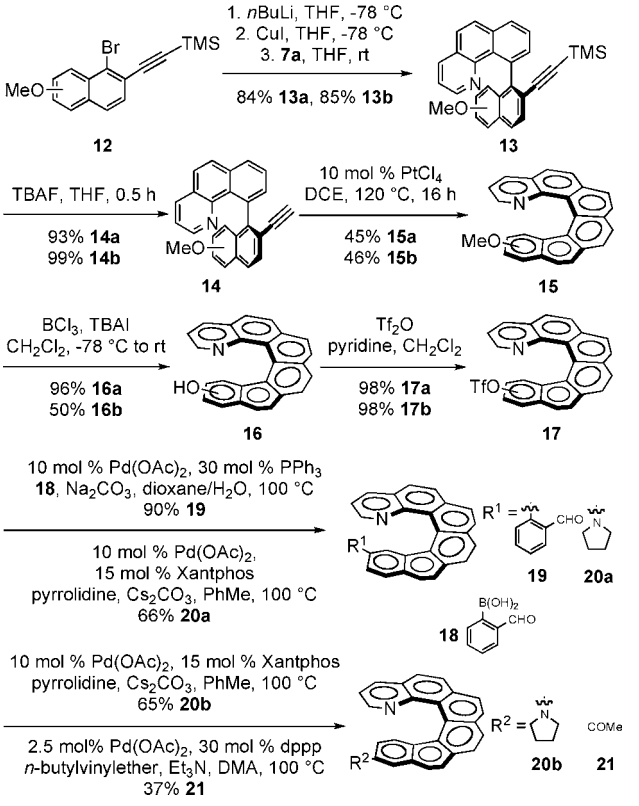
While carrying out additional optimization studies, we found that certain diene additives[30] were beneficial for the reaction, giving a significant rate enhancement. In a survey of dienes, (racemic) α-phellandrene was found to be the optimum additive. Using racemic α-phellandrene as an additive, the reaction temperature could be reduced to 80 °C giving **4** in comparable yield under otherwise identical conditions (Scheme 2).

Scheme 2. Optimized Cycloisomerization



Overall, 1-aza[6]helicene **4** was synthesized in four linear steps (or five steps overall) in a yield of ~35% from commercially available 1-bromo-2-naphthol. Furthermore, this chemistry was scalable, allowing us to easily prepare 1 g of **4** in a single run.

Scheme 3. Synthesis of Azahelicene Analogues



With our novel synthesis in hand, we prepared a range of substituted aza[6]helicenes (Scheme 3). In light of our previous demonstration of these helicenes in plastic electronic devices,[19,20] such derivatives offer a highly useful means to tune the requisite energy levels of a given azahelicene. Indeed, calculation of the HOMO and LUMO energy levels of helicene **4** and a 15-dimethylamino derivative **22** at the B3LYP/6-31+G(d,p) level of theory demonstrates that addition of an electron-donating amino substituent results in a drop in ionization potential by 0.49 eV, through alteration of the HOMO energy level, with little effect on the LUMO. This can be explained by inspection of the contribution of this substituent to the HOMO of **22** (Figure 2).

Bromoalkynes **12**[27] were coupled with bromobenzo[*h*]quinoline **7a** in good yield using a stoichiometric amount of CuI (Scheme 3). The TMS group was removed with TBAF, and the free alkynes **14** were subjected to the developed cycloisomerization conditions. The methyl ethers **15** were cleaved with BCl_3/TBAI, and the liberated hydroxyl groups converted to the corresponding triflates **17** in order to introduce further functionality via a variety of transition-metal-catalyzed processes. The cross-coupling reaction of triflate **17a** with boronic acid **18** proceeded without issue to give helicene **19** in good yield

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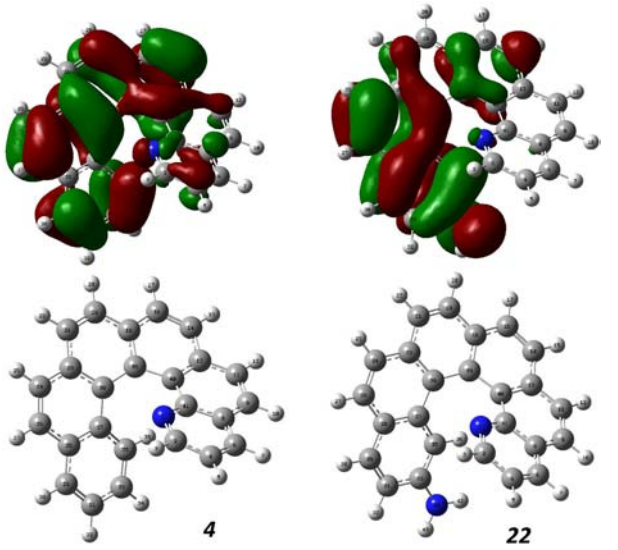


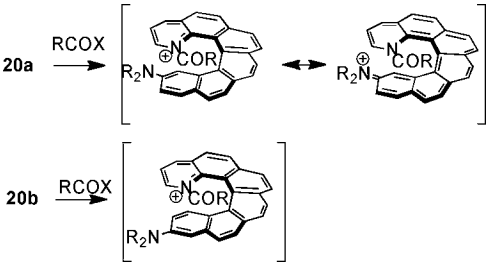
Figure 2. Comparison of the HOMOs of azahelicenes **4** and **22**.

(90%). Furthermore, the installation of the pyrrolidine unit using Buchwald–Hartwig chemistry or the introduction of carbonyl functionality via a Heck reaction were equally possible, giving helicenes **20a**/**20b** or **21** respectively.

With a highly efficient racemic synthetic route in hand, we next considered the potential for this strategy to be carried out asymmetrically, in order to isolate enantioenriched products directly. We found highly hindered biaryl **6** could be isolated as axially chiral atropisomers using semipreparative chiral HPLC. These enantiomers were highly stable to racemization: Heating single enantiomer R_a-**6** to 120 °C overnight in 1-nonanol resulted in no erosion of enantiopurity. In light of this, we felt there was significant scope to relay the stereochemical information from the chiral axis of alkyne **6** to the helicity of helicene **4**, using the developed methodology. Samples of enantiomer R_a-**6** (92% ee) and enantiomer S_a-**6** (94% ee) were subjected to the optimized cycloisomerization. To our delight, there was excellent relay of stereochemical information, with the helicene products *M*-**4** and *P*-**4** isolated in 90% and 92% ee, respectively. Assignments of absolute stereochemistry were made by comparison of experimentally obtained electronic circular dichroism (ECD) spectra with theoretically predicted ones (see the Supporting Information) as have been done previously.[31] We believe this is the first example of axial to helical chiral relay using such cycloisomerization chemistry. The apparent loss of stereochemical information is likely within error of the measurement, since product racemization[14] would not be significant under these conditions (see the Supporting Information). The high-fidelity transfer of stereochemical information from biaryl **6** to helicene **4** opens up the possibility of an enantioselective synthesis of azahelicenes using this strategy in the future via enantioselective synthesis of biaryl **6**.[32] Indeed, asymmetric transition-metal-catalyzed processes to prepare enantioenriched axially chiral biaryls are beginning to emerge.[33]

In conclusion, we have developed a rapid and robust strategy to prepare functionalized 1-aza[6]helicenes. In light of the high interest of these particular helicenes in catalysis, coordination chemistry, self-assembly, and materials science, we believe our route should enable material for further in-depth study. Furthermore, it is likely that a number of the derivatives prepared have interesting organocatalytic properties. Indeed, inspection of 15-pyrrolidine-substituted product **20a** and 14-pyrrolidine-substituted product **20b** reveals that in the former case the amino substituent is fully conjugated with the pyrido nitrogen, whereas it is not in the latter case (Scheme 4). As such, one could expect interesting differences in catalysis stemming from the study of such fully helically conjugated DMAP analogues. These and related studies are ongoing in our laboratories and will be reported in due course.

Scheme 4. Helical DMAP Analogues



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Supporting Information Available. Full experimental proceedures, compound characterization, reaction optimization, and racemization barriers.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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