Arenes

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Organocatalytic Enantioselective Construction of Polyaromatic Architectures**

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Dedicated to Professor Christian Roussel

arenes · atropisomerism · enantioselectivity · helical structures · organocatalysis

Aromaticity is a key concept in understanding the behavior of organic molecules, as it endows them with remarkable features in terms of stability, reactivity, and physical properties. Combining several aromatic rings within the same molecule will further influence their behavior. For this reason, polyaromatic structures have found applications not only in organic chemistry, but also in the field of supramolecular chemistry, materials science, and nanoscience. By definition, an aromatic ring is flat and most aromatic molecules are devoid of optical activity. However, crowded polyaromatic structures can display restricted bond rotations because of steric hindrance and become chiral molecules, thus exhibiting either axial or helical chirality (Figure 1). Although synthetic methods exist to prepare enantioenriched axially chiral biaryls[1] and helicenes,[2] progress is still needed in this field given the high value of these compounds.

In the past decade, organocatalysis has witnessed a tremendous evolution and has emerged has a powerful tool for the creation of complex molecules possessing one or several stereogenic centers.[3] Nevertheless, the construction of other types of chirality (e.g. axial or helical chirality) has received much less attention. The lack of investigation in this area could be explained by the difficulty to build aromatic rings by organocatalysis. In two recent reports, the groups of List[4] and Sparr[5] have disclosed proofs of concept that organocatalysis is a suitable tool for attaining complex polyaromatic architectures which exhibit helical and axial chirality, respectively. In both cases, reaction sequences may be envisioned where central chirality is controlled at first, with a subsequent aromatization step proceeding with efficient chirality interconversion.[6]

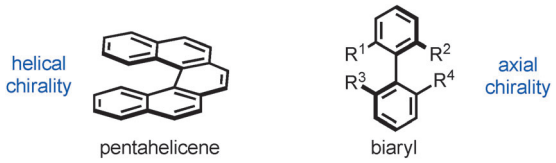
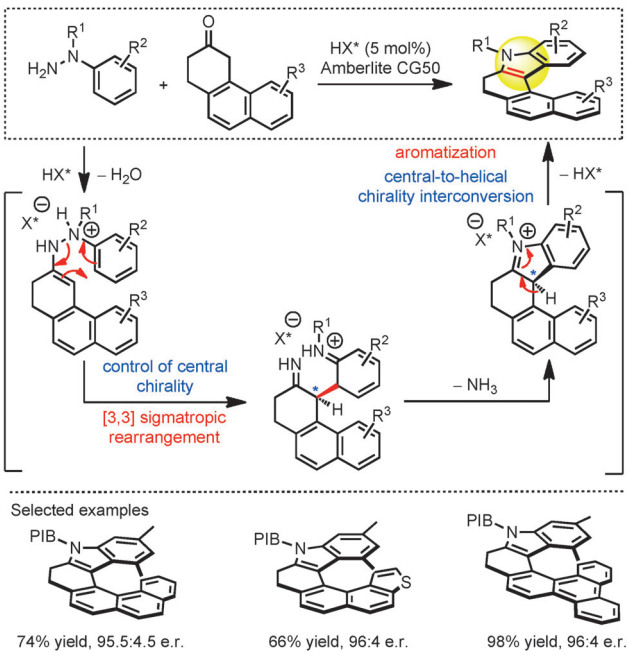


Figure 1. Helical and axial chirality.

As a follow-up study to their previous publication on the enantioselective Fischer indole synthesis with construction of central chirality,[7] List and co-workers described the application of the same reaction to the first enantioselective organocatalytic synthesis of azahelicenes (Scheme 1).[4] Fischer indole synthesis is known to proceed through an acid-catalyzed [3,3] sigmatropic rearrangement of an enehydrazine intermediate into a bis(imine) by fragmentation of the nitrogen–nitrogen bond. In the presence of a suitably selected chiral Brønsted acid, the stereogenic center at C3 can be enantioselectively forged. After loss of a molecule of ammonia, the subsequent aromatization destroys the stereogenic center, but when the ketone substrate bears a large



Scheme 1. Organocatalytic approach to helicenes.[4] PIB = *p*-iodobenzyl.

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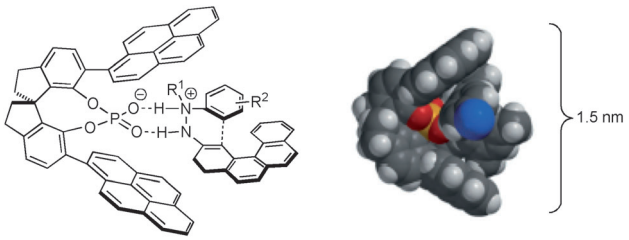


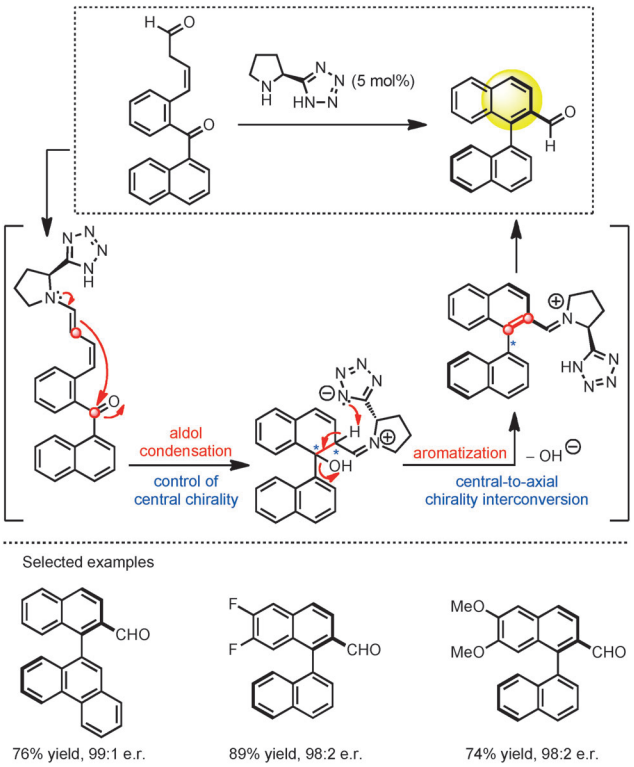
Figure 2. Rationale for the design of the new phosphoric acid catalyst and three-dimensional model of the catalyst with the enehydrazine intermediate.[4]

aromatic substituent, this step results in the formation of a configurationally stable helicene with a central-to-helical interconversion of chirality.

To catalyze this transformation, the authors relied on SPINOL-derived phosphoric acids (Figure 2). To control the enantioselectivity of the helicene formation a new catalyst had to be designed, a catalyst which would enable long-range control on the nanometer scale—an unusually large scale for catalytic organic transformations. The π–π stacking interaction between the large pyrene 3,3′-substituents of the catalyst and the polyaromatic system of the reactive intermediate are supposed to hold the latter ones in a chiral nanometer-sized pocket, thereby inducing the screw sense of the helix.

The choice of a *p*-iodobenzyl moiety as a protecting group on the hydrazine starting material and the addition of the weakly acidic Amberlite CG50 to ensure catalyst turnover were also key to the success of the reaction. The complete oxidative aromatization of the product, along with the synthesis of a diazahelicene by a double Fischer indolization using the same approach, are also discussed in the same publication.

Independent of the work from the group of List, Link and Sparr described an enantioselective catalytic aldol reaction, from easily accessed ketoaldehydes, with subsequent central-to-axial chirality interconversion to afford highly enantioenriched binaphthyl-2-carbaldehydes (Scheme 2).[5] They performed an intramolecular addition of a configurationally stable *E*,*Z*-dienamine to the tethered aromatic ketone, thus leading to the formation of a chiral center, which, after dehydratation and elimination of the catalyst, provided the biaryl compound with high enantiomeric excess. The use of a catalytic amount (5 to 10 mol%) of a pyrrolidinyl-tetrazole catalyst gave the best selectivity (99:1 at RT) even when the reaction temperature was increased to 60 °C (94:6). It is worth noting that among the other aminocatalysts screened in the study, only proline gave reasonable levels of enantioselectivity, thus highlighting the importance of the presence of an acidic proton in the structure of the catalyst. Indeed, the assistance of the deprotonated nitrogen atom of the tetrazole ring might play an important role during the aromatization step. Even though a few innovative reports on the organocatalytic control of axial chirality of biaryls[8] or other strained systems[9] have appeared in the literature in the recent years, Sparr's work seems to be the first instance of the construction of an aromatic ring with concomitant control of axial chirality through an organic catalyst. The possibility of central-to-axial



Scheme 2. Organocatalytic atroposelective aldol condensation.[5]

chirality interconversions was hypothesized by Berson almost 60 years ago[10] and the first experimental evidence for the synthesis of naphtylquinoline atropisomers was provided by Meyers in 1984.[11] However, the first occurrence of the combination of enantioselective catalysis with central-to-axial chirality interconversion was disclosed only in 2011 by Thomson and co-workers, who reported a rhodium-catalyzed three-step enantioselective synthesis of biphenols.[12]

To conclude, the groups of List[4] and Sparr[5] have described the organocatalytic synthesis of complex enantioenriched polyaromatic structures, bearing helical or axial chirality, from simple building blocks. These innovative reports undeniably open the way for unexplored possibilities and bring aromatics into the third dimension, by converting flat, achiral molecules into complex chiral molecular polyaromatic architectures.

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