

Catalytic Arene-forming Aldol Condensation: Stereoselective Synthesis of Rotationally Restricted Aromatic Compounds

Vincent C. Fäseke, Reto M. Witzig, Achim Link, Dominik Lotter, and Christof Sparr[§]

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Abstract: By taking inspiration from the fascinating biosynthetic machinery that creates aromatic polyketides, our group investigates analogous reactions catalyzed by small molecules. We are particularly captivated by the prospects of intramolecular aldol condensation reactions to generate different rotationally restricted aromatic compounds. In a first project of our independent research group, a highly stereoselective amine catalyzed synthesis of axially chiral biaryls, tertiary aromatic amides and oligo-1,2-naphthylenes has been developed. In this article, we outline the twists and turns for our escape from the aromatic flatland to structurally intriguing chiral arene scaffolds relevant for various fields of application.

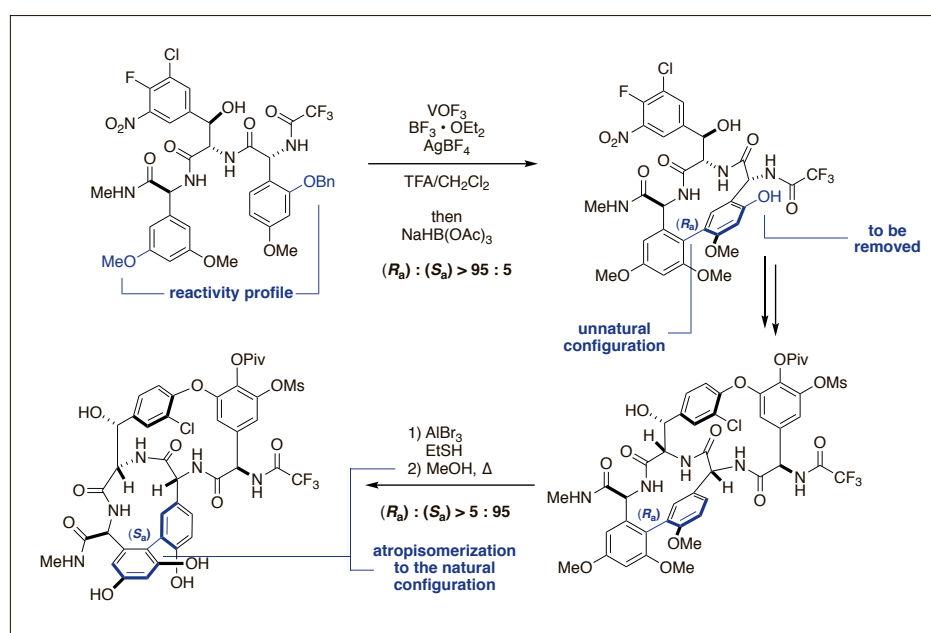
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Christof Sparr was born and raised in Appenzell (Switzerland). After working at F. Hoffmann-La Roche AG (Basel), he studied at the Zürcher Hochschule Winterthur and subsequently at the ETH Zürich, where he earned a Masters degree in 2008. He then joined the group of Prof. Ryan Gilmour and was awarded his PhD in 2011. After postdoctoral work with Prof. Dieter Seebach and subsequently with Prof. Steven V. Ley in Cambridge, UK, he became a habilitand mentored by Prof. Karl Gademann. Since 2016, he works as Assistant Professor at the University of Basel with a research program focussing on synthetic organic chemistry. He is recipient of the ETH silver medal, an SNSF starting grant and the Werner Prize 2017.

Due to their favorable and well-defined structure, configurationally stable stereoisomers resulting from the restricted rotation about a single bond (atropisomers) have found widespread use across several disciplines. The binaphthalene moiety surely occupies a privileged position, especially in the area of stereoselective catalysis.^[1] However, atropisomerism is also a key aspect in other fields, such as natural products research, as exemplified by the prominent antibiotic vancomycin with

a rotationally restricted biaryl motif.^[2] In the case of biaryls, steric interactions of three or four *ortho*-substituents provide pronounced barriers to rotation, often above 120 kJmol⁻¹, and their stereoisomers are hence separable and configurationally stable. Nevertheless, the separation of racemic mixtures to access atropoenantiomers in stereoisomerically pure form is usually impractical and associated with high costs. Furthermore, if prepared with substrate stereocontrol, diastereomers of rotation-



Scheme 1. Atropisomerization approach in the total synthesis of vancomycin by Evans and co-workers.^[2b,c]

*Correspondence: Prof. Dr. C. Sparr
University of Basel
Department of Chemistry
St. Johannis-Ring 19
CH-4056 Basel
E-mail: christof.sparr@unibas.ch

ally restricted compounds are often not accessible or only in trace amounts. This scenario is illustrated by the total synthesis of vancomycin by Evans and co-workers (Scheme 1). A substrate-controlled oxidative biaryl coupling under precisely de-

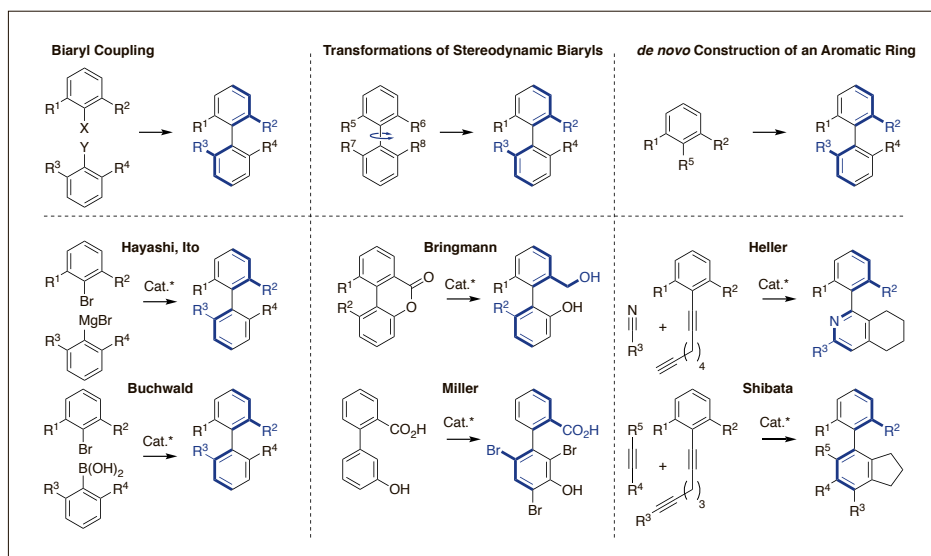
defined reaction conditions led to full atroposelectivity, but to the undesired atropisomer with the unnatural (R_a)-configuration.^[2b,c] For their successful synthesis, the Evans group therefore relied on a thermal atropisomerization of a later cyclic intermediate

with smaller *ortho*-substituents. At a temperature that did not lead to decomposition, the equilibration selectively favored one stereoisomer, which was the desired intermediate with the natural configuration. As these factors complicate the synthesis of atropisomers and since highly *ortho*-substituted biaryls may not atropisomerize at a viable temperature, catalyst-controlled methods are required to prepare the different stereoisomers selectively.

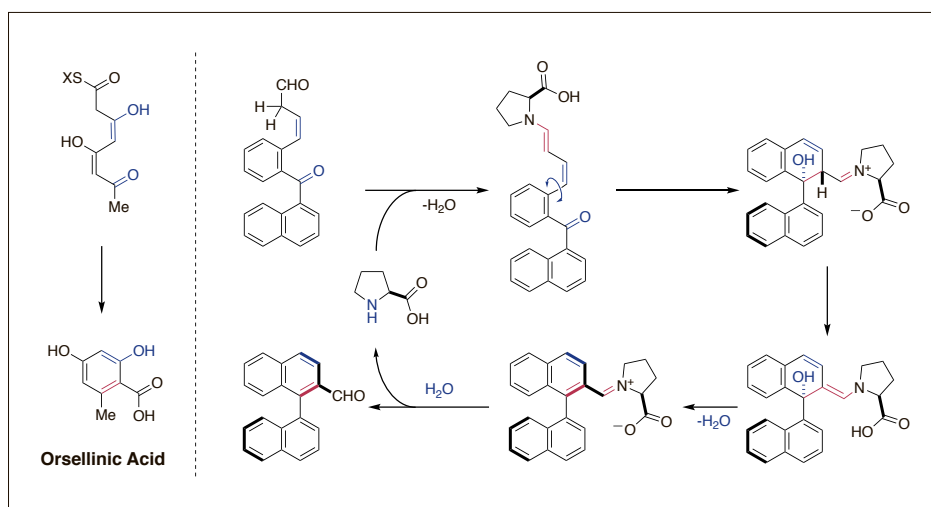
Besides kinetic resolution and desymmetrization,^[3] three main strategies have been developed for the catalyst-controlled atroposelective synthesis of biaryls (Scheme 2). Examples for biaryl cross-coupling reactions to directly form the rotationally restricted bond by using chiral catalysts include the atroposelective Kumada coupling reported by Hayashi and Ito, as well as the enantioselective Suzuki cross-coupling disclosed by Buchwald.^[4,5] In an alternative strategy, stereodynamic biaryls which are in equilibrium under the reaction conditions are converted into configurationally stable products. For instance, the biaryl lactones disclosed by Bringmann *et al.*, where planarization leads to an increased ground state energy and therefore to a lower barrier to rotation, were selectively converted into rotationally restricted lactone-opened products.^[6] Contrariwise, the tribromination catalyzed by short-peptides reported by Miller *et al.* represents the selective introduction of *ortho*-substituents that lead to larger steric interactions in biaryl rotation.^[7] A third strategy directly constructs a new aromatic ring in an atroposelective reaction by the use of chiral catalysts; a concept that was pioneered by Heller, Shibata, and Tanaka with [2+2+2]-cycloaddition reactions of tethered dialkynes.^[8]

As the *de novo* construction of an aromatic ring appears as a particularly promising strategy that potentially allows to develop methods with high generality, we examined processes based on the biosynthesis of aromatic compounds. We became especially interested in the biosynthesis of aromatic polyketides, where poly- β -carbonyl precursors are initially assembled to a specific length and then folded selectively by aromatase/cyclase proteins to catalyze selective aldol condensation reactions.^[9] As an astonishing number of relevant natural products are assembled by this biosynthetic machinery, we were intrigued by the possibility to transfer this reaction manifold into the context of atroposelective catalysis. It is pertinent to note that this endeavor profits from groundbreaking biomimetic studies by Collie, Birch, Harris, Barrett, Yamaguchi and many more, which support its feasibility for a broad range of compounds.^[10]

By considering the poly- β -carbonyl precursor for the prototypical aromatic

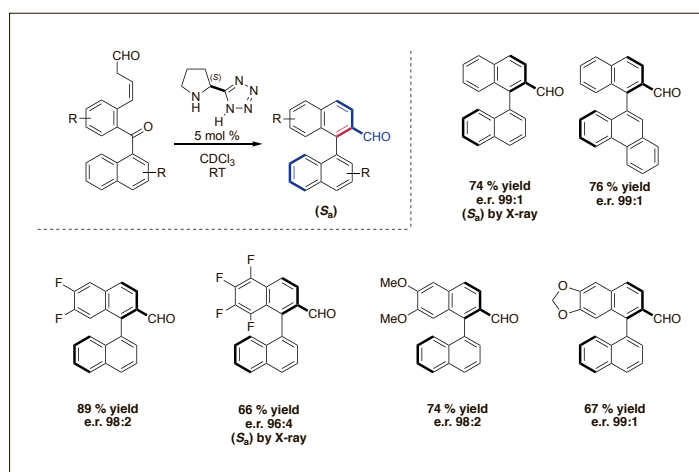


Scheme 2. Selected strategies for the catalytic enantioselective synthesis of atropisomeric biaryls.



Scheme 3. Working hypothesis of the stereoselective, amine-catalyzed arene-forming aldol condensation.

Scheme 4. Scope of the stereoselective arene-forming aldol condensation for biaryls.^[11]



polyketide orsellinic acid and its tautomeric forms, alkene and aryl substitution leads to a configurationally stable binaphthalene system upon an arene-forming aldol condensation (Scheme 3). We assumed that activation of an aldehyde substrate with a chiral amine catalyst forms a (*Z,E*)-dienamine intermediate for an intramolecular aldol addition, which subsequently affords a cyclic iminium salt. Dehydration, conceivably *via* another dienamine, results in the formation of a new aromatic ring and consequently the binaphthalene scaffold. Ultimately, we envisaged that enantioenriched compounds are formed by the induction of the stereochemical information of the catalyst into the axially chiral products.

To test this hypothesis, a first substrate was prepared from 1-naphthaldehyde and treated with L-proline as catalyst.^[11] Upon addition of the catalyst, the desired 1,1'-binaphthalene-2-carbaldehyde was formed with a promising atroposelectivity of 88:12, which was further improved to an e.r. of 99:1 by using its tetrazole derivative (Scheme 4).^[12] With 5 mol% (*S*)-pyrrolidinyl tetrazole, the reaction scope comprises derivatives with electron withdrawing and donating groups and provides tri-*ortho*-substituted biaryls in good yields and notable selectivity.

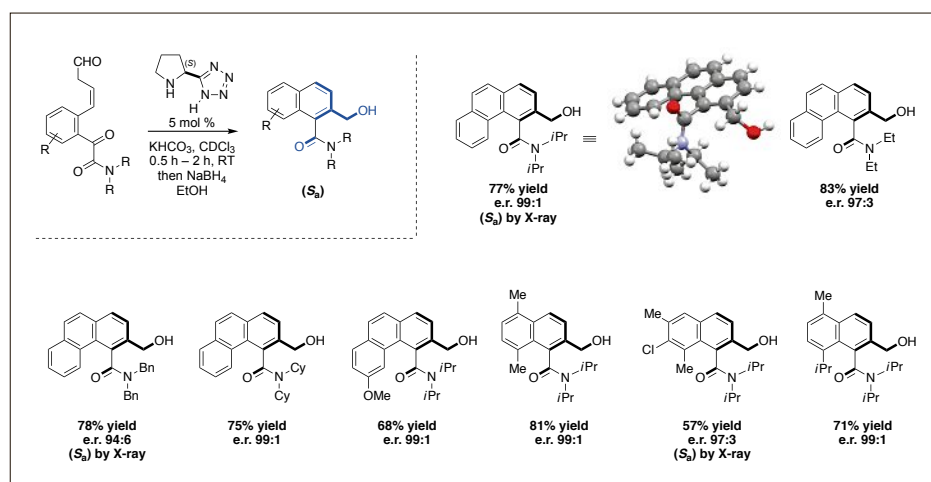
To confirm the generality of this strategy, we next studied axially chiral aromatic amides, as they are of importance in medicinal chemistry and may serve as structurally distinct atropisomeric scaffold for drug discovery.^[13] By replacing the 1-naphthyl group with a tertiary amide, an activated α -ketoamide substrate was considered as precursor for configurationally stable substituted aromatic amides with an interesting molecular topology (Scheme 5).^[14] Addition of the (*S*)-pyrrolidinyl tetrazole catalyst triggered the prompt formation of the desired rotationally restricted aromatic formyl amide, which was complete within two hours at ambient temperature. To increase the configurational stability of the products and therefore the scope of the method, we coupled the aldol condensation with an *in situ* reduction step, thus providing the hydroxy derivatives in high yields and exceptional atroposelectivity. The reaction was amenable to various amide substituents for the synthesis of phenanthrene- and naphthamides.

Motivated by the satisfactory outcome of these reactions, we considered the synthesis of compounds with more than one stereogenic axis. As the 1,1'-binaphthalene-2-carbaldehydes were prepared from naphthalene-1-carbaldehyde and with catalyst control over the configuration of the rotationally restricted bond, an iterative overall insertion of a naphthylene unit across the naphthalene/carbaldehyde bond

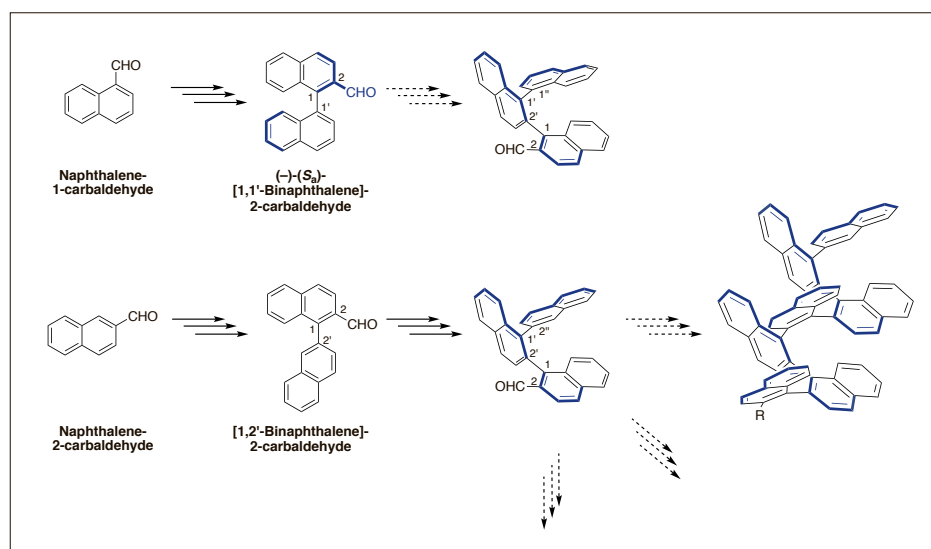
was considered (Scheme 6). To provide a regular oligomeric unit, naphthalene-2-carbaldehyde was selected as terminal group, which first leads to a stereodynamic di-*ortho*-substituted binaphthalene with a low rotational barrier. A subsequent catalyst-controlled synthesis of a configu-

rationaly stable ternaphthalene would establish a starting point for different diastereomeric structures with interesting topologies, such as the shown helically shaped oligo-1,2-naphthylene.

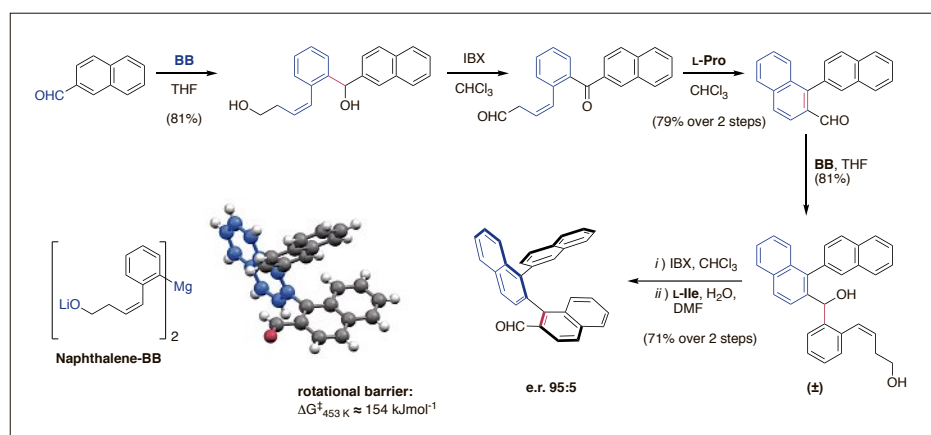
Configurationally stable helically shaped aromatic oligomers are expected



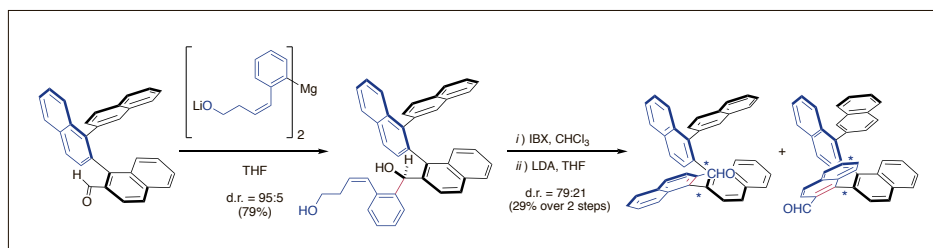
Scheme 5. Synthesis of axially chiral aromatic amides by the stereoselective arene-forming aldol condensation.^[14]



Scheme 6. Synthetic strategy for the catalyst-controlled synthesis of oligo-1,2-naphthylenes.



Scheme 7. Iterative synthesis of an enantioenriched ternaphthalene by a building block addition/oxidation/aldol condensation sequence.^[17]



Scheme 8. Synthesis of configurationally stable oligo-1,2-naphthylene diastereoisomers.^[17]

to be of particular interest, as different substituents can be predictably placed into a specific spatial arrangement.^[15] While various structurally well-defined aromatic compounds have been reported to be of great use for various applications,^[16] we envisaged the iterative synthesis of oligo-naphthylenes with three *ortho*-substituents for each binaphthyl subunit. To efficiently assemble these oligomers, we implemented a strategy of a repeated building-block addition, *in situ* oxidation, aldol condensation sequence (Scheme 7).^[17] To avoid protecting group manipulations, an organometallic lithium alkoxide reagent was utilized as naphthalene building block (BB). After the formation of a first aromatic ring to provide the stereodynamic binaphthalene carbaldehyde, the addition of a second building block to the growing chain and a subsequent *in situ* oxidation and the treatment with *L*-isoleucine as catalyst induced an atropenantioselective arene-forming aldol condensation to form a ternaphthalene with exceptionally high configurational stability (154 kJmol⁻¹).

In order to investigate a substrate-controlled synthesis of oligo-1,2-naphthylene diastereoisomers, attachment of another building block and *in situ* oxidation was followed by the addition of LDA. Intriguingly, the atropodiastereoisomers were formed in a ratio of 79:21 and were separable by preparative TLC. The isolated quaternaphthalenes were individually characterized to confirm their high configurational stability, while stereoisomer interconversion was never observed.

Summary and Outlook

In conclusion, the stereoselective arene-forming aldol condensation was found to be a versatile synthetic concept to prepare distinct rotationally restricted aromatic compounds with high selectivity under operationally simple conditions by the use of chiral amine catalysts. The exceptional selectivity observed in the atroposelective synthesis of atropisomeric biaryls and aromatic amides is conceivably the result of a structurally confined transition state of the intramolecular aldol addition step. The oligo-1,2-naphthalene atropodiastereoisomers are expected to serve as

an ideal scaffold for the predictable spatial positioning of groups attached to the naphthalene units. Ongoing studies focus on the synthesis of tetra-*ortho*-substituted biaryls and the development of catalyst-controlled atropodiastereoselective reactions for a programmable synthesis of topologically interesting molecular frameworks.

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