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Stereoselective Arene-Forming Aldol Condensation: Synthesis of Configurationally Stable Oligo-1,2-naphthylenes

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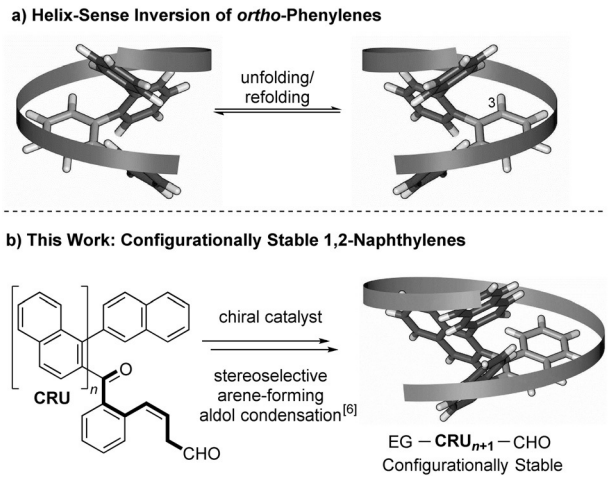
Dedicated to Professor Herbert Mayr

Abstract: *Structurally well-defined oligomers are fundamental for the functionality of natural molecular systems and key for the design of synthetic counterparts. Herein, we describe a strategy for the efficient synthesis of individual stereoisomers of 1,2-naphthylene oligomers by iterative building block additions and consecutive stereoselective arene-forming aldol condensation reactions. The catalyst-controlled atropoenantioselective and the substrate-controlled atropodiastereoselective aldol condensation reaction provide structurally distinct ter- and quaternaphthalene stereoisomers, which represent configurationally stable analogues of otherwise stereodynamic, helically shaped ortho-phenylenes.*

The properties of helically shaped arylenes are intrinsically connected to their stereodynamic behavior. In the parent phenylenes, rapid stereoisomerization processes are observed, from which several applications profit.[1] However, structurally well-defined, configurationally stable helical systems are considered to be particularly valuable chiral motifs, as substituents can be placed into a predictable spatial relationship and the overall character can be correlated to a specific molecular arrangement.[2] In prototypical *ortho*-phenylenes, the 1,2′-di-*ortho*-substituted biaryl subunits are not conformationally restricted, and structural reorganizations, such as helix-sense inversions, occur rapidly at room temperature (Scheme 1 a).[3] The most recent efforts to stabilize the helical folding mode of *ortho*-phenylenes, enantioenriched by conglomerate crystallization, are based on one-electron oxidations, thereby leading to a half-life of racemization of 44 h at 10 °C.[4]

In contrast, if configurational stability can be achieved by increasing each aryl–aryl torsional strain, the shape of the entity and the helix sense is not dictated by constitutional repeating units (CRUs), end groups (EGs), or crystallization processes, but can be controlled by transcribing the stereochemical information encoded in a chiral catalyst.[5] By considering the analogy to axially chiral biaryls, we asked the question whether configurationally stable helical arylenes could be prepared by the formal addition of a third *ortho*-substituent at the 3-position. More specifically, we expected that stereoisomerization processes would be dramatically suppressed when 1,2-naphthylene was used as the CRU, and discrete stereoisomers would become isolable (Scheme 1 b). The key incentive was the premise of achieving catalyst stereocontrol by constructing the CRUs with the stereoselective arene-forming aldol condensation developed in our group.[6]



Scheme 1. a) Helix-sense inversion of *ortho*-phenylenes by unfolding and refolding processes. b) Catalytic stereoselective aldol condensation to form configurationally stable 1,2-naphthylene oligomers (a stereoisomer with a helical secondary structure is shown). CRU: constitutional repeating unit; EG: end group.

For the efficient assembly of the oligomer, we devised an iteration strategy based on the addition of an organometallic C_{10}-naphthylene building block to the preceding aryl carbaldehydes, followed by an in situ double oxidation to form ketoaldehydes for the aldol condensation steps. The precursor (*Z*)-4-(2-bromophenyl)but-3-en-1-ol (**2**) was prepared by a mono-Sonogashira cross-coupling reaction followed by a *Z*-selective hydrogenation (Scheme 2).[7] To circumvent protecting-group manipulations, we explored the possibility of forming a metal alkoxide prior to halogen–metal exchange. The efficient Br–Li exchange of a preformed magnesium alkoxide, leading to transmetalation as described by Kato et al., appeared to be particularly attractive.[8] Compound **2** was treated with nBu$_2$Mg at 0 °C for 45 min, followed by the addition of nBuLi at the same temperature. The resulting mixed-metal species forms putative magnesiate intermediates to furnish the corresponding diaryl magnesium lithium alkoxide **3** with an ideal stability and reactivity for carbonyl

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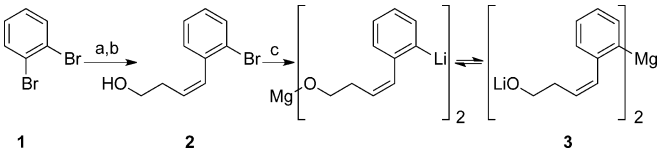
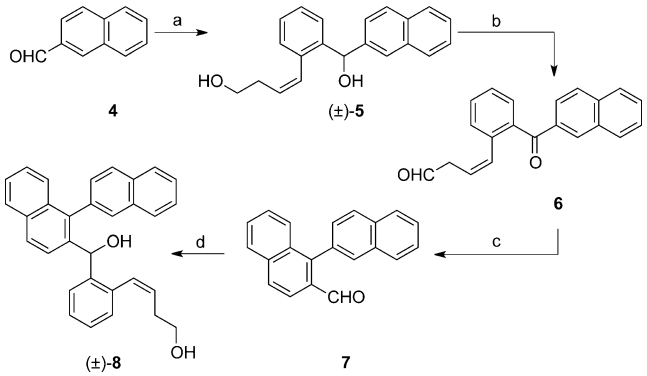


Scheme 2. Synthesis of building block **3**. a) 3-Butyn-1-ol, CuI, [Pd-(PPh_3)$_4$], *i*Pr_2NH, reflux, 60%; b) Ni(OAc)$_2$·4 H_2O, $NaBH_4$, EtOH, H_2, ethylenediamine, RT, 95%; c) *n*Bu_2Mg, THF, then *n*BuLi, 0°C; the in situ prepared solution of reagent **3** was used directly as building block for chain elongation.

addition reactions. Owing to these favorable characteristics, we employed reagent **3** as a building block for each chain-elongation step.

To provide a regular 1,2′-oligomer connectivity, a 2-naphthyl end group was selected as the terminus. The addition of building block **3** to naphthalene-2-carbaldehyde (**4**) led to a first chain elongation to provide diol (±)-**5** in 81% yield (Scheme 3). The following in situ double oxidation with

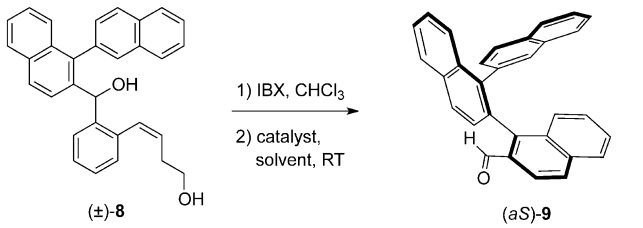


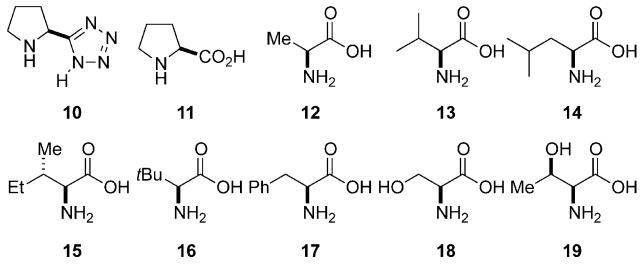
Scheme 3. Synthesis of substrate precursor (±)-**8**. a) **3**, THF, 0°C, 81%; b) IBX, $CHCl_3$, 60°C; c) L-proline, $CHCl_3$, RT, 79% over two steps; d) **3**, THF, 0°C, 81%. IBX: 2-iodoxybenzoic acid.

IBX formed a highly reactive ketoaldehyde **6** poised for the first arene-forming aldol condensation. Filtration of the reaction mixture and treatment with catalytic amounts of L-proline gave 1,2′-binaphthalene-2-carbaldehyde (**7**)[9] in 79% yield over two steps. The second building block addition allowed the preparation of diol (±)-**8**, the substrate precursor of the catalyst-controlled atropoenantioselective arene-forming aldol condensation.

A double in situ oxidation of (±)-**8** led to a ketoaldehyde stable enough for a rapid solvent switch (Table 1). To our delight, the addition of pyrrolidinyltetrazole catalyst **10** resulted in a small amount of the desired axially chiral ternaphthalenecarbaldehyde (*aS*)-**9** with an excellent first atroposelectivity of 92:8 (Table 1, entry 1). The enantiocontrol could be improved to 99:1 by using a DMF/H_2O mixture as solvent; however, the yield remained low (entry 2). As a result of the poor catalytic performance of **10**, even at high catalyst loading, we reinvestigated inexpensive natural amino acids as catalysts for this arene-forming aldol condensation. With L-proline (**11**) as the catalyst, the DMF/H_2O mixture

Table 1: In situ double oxidation[a] and optimization of the stereoselective arene-forming aldol condensation to form ternaphthalene (*aS*)-**9**.[b]





Entry	Catalyst	Solvent	Yield[c] [%]	e.r.[d]
1	**10**	$CDCl_3$	< 5	92:8
2	**10**	DMF/H_2O[e]	24	99:1
3	**11**	$CDCl_3$	0	–
4	**11**	DMF/H_2O[e]	12	96:4
5	**12**	DMF/H_2O[e]	39	83:17
6	**13**	DMF/H_2O[e]	35	91:9
7	**14**	DMF/H_2O[e]	60	88:12
8	**15**	DMF/H_2O[e]	**71**	**95:5**
9	**16**	DMF/H_2O[e]	55	93:7
10	**17**	DMF/H_2O[e]	56	80:20
11	**18**	DMF/H_2O[e]	56	74:26
12	**19**	DMF/H_2O[e]	69	78:22

[a] The in situ double oxidation reactions were performed with 70.0 μmol substrate precursor (±)-**8** and 350 μmol IBX in $CHCl_3$ at 60°C. [b] The aldol condensation reactions were performed after filtration of the resulting mixture and an optional solvent switch with 40.0 mol% catalyst in 4.7 mL solvent at RT for 72 h. [c] Yield of isolated product over two steps. [d] Determined by HPLC. [e] 4.0 mL DMF and 700 μL H_2O.

was confirmed as the solvent of choice, and the low catalytic performance of secondary amines was corroborated (entries 3 and 4). In contrast, a clear improvement in yield was observed with primary amines L-alanine (**12**), L-valine (**13**), and L-leucine (**14**), while the stereoselectivity remained at a remarkable level (entries 5–7). We assume that the consistently high stereocontrol is the consequence of a significant degree of preorganization of the substrate and that steric encumbrance of the 1,2′-binaphthalen-2-yl (phenyl) ketone leads to the observed differences in the catalytic activity of secondary and primary amines. Intriguingly, the use of L-isoleucine (**15**) resulted in an optimal combination of yield and selectivity (e.r. 95:5, entry 8),[10] whereas L-*tert*-leucine (**16**) with a larger side chain was less efficient (entry 9). Amino acids with an aromatic or polar side chain also displayed a lower catalytic performance, and L-isoleucine (**15**) was identified as the ideal catalyst (entries 10–12 versus entry 8). With optically active ternapthalene in hand, we next examined the configurational stability of (*aS*)-**9**. An exceptionally high rotational barrier of $\Delta G^{\ddagger}_{453\,K} = 154\ kJ\,mol^{-1}$ was determined, supporting our hypothesis that the tri-*ortho*-substituted aryl–aryl bonds of

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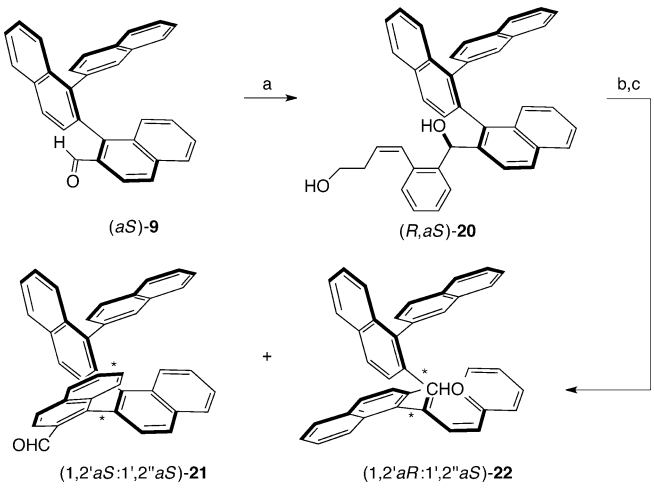
oligo-1,2-naphthylenes are sufficiently restricted in rotation to form discrete stereoisomers, even well above room temperature.

Motivated by these results, we became intrigued by the possibility of assembling oligo-1,2-naphthylenes with more than one element of axial chirality. A third building block was added to ternaphthalene in 79% yield and with 95:5 enantioface discrimination (Scheme 4). The diastereoisomers (*R*,*aS*)-



Scheme 4. Synthesis of the two quaternaphthalene atropodiastereoisomers under substrate stereocontrol. a) **3**, THF, 0°C, d.r. 95:5, 79%; b) IBX, $CHCl_3$, 60°C; c) LDA, THF, −30°C→RT, d.r. 79:21 (**22**/**21**), 29% over two steps. Compounds **9**, **20**, **21**, and **22** were studied by X-ray crystallography.[13] LDA: lithium diisopropylamide.

20 and (*S*,*aS*)-**20** converge in the subsequent oxidation step. However, the high selectivity provides an indication of the well-defined structure of the ternapthalene (*aS*)-**9**. As expected, based on the solid-state structure of (*aS*)-**9** ($\phi_{CC\text{-}CHO} = -173°$), a selective *re*-face addition was obtained, as confirmed by X-ray crystallographic analysis of (*R*,*aS*)-**20**.[11] After in situ double oxidation, we explored the accessibility and configurational stability of the quaternaphthalene atropodiastereoisomers. The arene-forming aldol condensation was, therefore, performed under substrate stereocontrol using LDA. Satisfyingly, both atropodiastereoisomers (1,2′*aS*:1′,2″*aS*)-**21** and (1,2′*aR*:1′,2″*aS*)-**22** were formed with a d.r. of 79:21. The stereoisomers could be effortlessly separated by preparative TLC, and routine analysis could be performed due to the typically high solubility of helical arylenes. The absolute configuration of the compounds was established by comparison of the measured and calculated CD spectra of compounds **9**, **21**, and **22**, which displayed exceptionally strong Cotton effects.[12]

Having prepared both discrete quaternaphthalene atropodiastereoisomers, we examined the differences in the ring current effects observed in the ^{1}H NMR spectra to gain insight into their structures in solution. The aldehyde proton of **22** experiences a strong characteristic shielding ($\delta_H =$ 8.0 ppm; $\Delta\delta_H$(**21**$_{CHO}$-**22**$_{CHO}$) = 2.0 ppm), while the naphthalene signals of **21** were distributed over a range of 2.2 ppm (δ_H = 8.0–5.8 ppm). As a result of the lower *ortho*-substitution of the end group, two rotamers were detected by NMR spectroscopy, thereby serving as a gauge for interactions operative between the oligomer units. Smaller congeners display a balanced distribution, whereas atropodiastereomer **21** with a parallel arrangement of the first and the fourth naphthalene groups shows a preference for one of the rotamers (for **8**, **9**, and **20** = 1.0:1.1; for **21** = 1.0:1.7; for **22** = 1.0:1.3).[9]

X-ray crystallographic analysis of both quaternaphthalenes confirmed the molecular arrangement of **21** and **22** (Figure 1).[13] A distinct right-handed helical secondary struc-

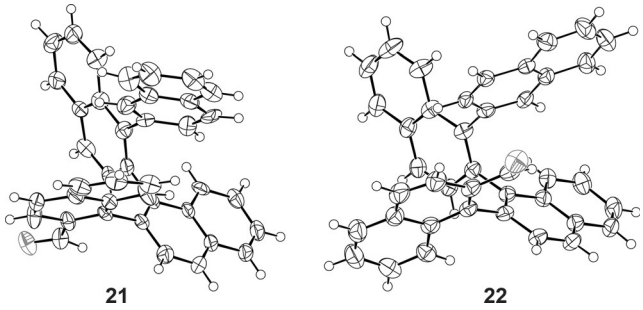


Figure 1. X-ray crystal structures of the 1,2-naphthylene atropodiastereoisomers **21** and **22** with opposite configuration of one of the two chirality axes. Thermal ellipsoids are drawn at the 50% probability level.[13]

ture of **21** with three naphthalene units to each turn was established. In the congested *P*-helix, the average biaryl torsion angle is 66° and interatomic distances are as short as 3.3 Å. The inner benzene moieties are arranged analogous to *ortho*-phenylenes in the solid state, where self-organization leads to the preferred helical coil. In contrast, quaternaphthalenecarbaldehydes **21** and **22** confirm that individual 1,2-naphthylene diastereoisomers with a different relative configuration of the chirality axes are isolable and configurationally stable at room temperature.[14]

In conclusion, we have developed an efficient assembly approach for the selective synthesis of discrete oligo-1,2-naphthylene stereoisomers. A mixed-metal species obtained by a practical transmetalation strategy served as the building block for the protecting-group-free introduction of naphthylene precursor units to enable rapid chain elongation. The arene-forming aldol condensation allowed a stereoselective synthesis of structurally distinct isomers of ter- and quaternaphthalenes. Enantiocontrol was achieved by using a natural amino acid as catalyst, while the preparation of both individual atropodiastereoisomers with two elements of axial chirality was based on a substrate-controlled arene-forming aldol condensation. The unique structure of oligo-1,2-naphthylenes[15] leads to full configurational stability at room temperature. The shape, such as the *P*-helix secondary structure,[16] is not encoded in the building blocks, but is transcribed from L-isoleucine with 95:5 enantioselectivity. As a result of the well-defined molecular structure, we expect that oligo-1,2-naphthylenes will serve as scaffolds to predictably place substituents into a preferred spatial arrangement. In ongoing studies, we are examining catalyst-controlled

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atropodiastereoselective arene-forming aldol condensations as well as the preparation of longer oligonaphthylenes with various substitution patterns.

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Keywords: aldol reactions · atropisomerism · configurational stability · oligonaphthylenes · stereoselectivity

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[9] The oligomer with a 2-naphthyl end group was prepared to obtain a regular oligomer constitution, thereby resulting in a terminal binapthyl bond with di-*ortho*-substitution not restricted in rotation at room temperature.

[10] Scale-up to 1.39 mmol gave ternaphthalene (*aS*)-**9** in 65% yield and the same enantioselectivity.

[11] As a result of the *trans* aryl aldehyde conformation of **9**, as drawn in Scheme 4 and confirmed by X-ray analysis, the *si*-face is sterically shielded by the terminal naphthalene group; see Ref. [13].

[12] See the Supporting Information for further information.

[13] CCDC 1405205 [(±)-**9**], CCDC 1405204 [(±)-**20**], CCDC 1405203 [(±)-**21**], and CCDC 1405206 [(1,2′*aR*:1′,2″*aS*)-**22**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. As only racemic single crystals could be obtained for **9**, **20**, and **21**, and since the data for **22** was not sufficient to assign the absolute configuration with adequate reliability, we based the assignment on CD spectroscopy.

[14] Interconversion of diastereoisomers **21** and **22** was not observed over the entire course of our studies, giving further support for the notable configurational stability of oligo-1,2-naphthylenes.

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