# Catalyst-Controlled Stereodivergent Synthesis of Atropisomeric Multiaxis Systems

Dominik Lotter, Alessandro Castrogiovanni, Markus Neuburger, and Christof Sparr*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

Ⓢ Supporting Information

ABSTRACT: Molecular scaffolds with multiple rotationally restricted bonds allow a precise spatial positioning of functional groups. However, their synthesis requires methods addressing the configuration of each stereogenic axis. We report here a catalyst-stereocontrolled synthesis of atropisomeric multiaxis systems enabling divergence from the prevailing stereochemical reaction path. By using ion-pairing catalysts in arene-forming aldol condensations, a strong substrate-induced stereoprefer- ence can be overcome to provide structurally well-defined helical oligo-1,2-naphthylenes. The configuration of up to four stereogenic axes was individually catalyst-controlled, affording quinquenaphthalenes with a unique topology.
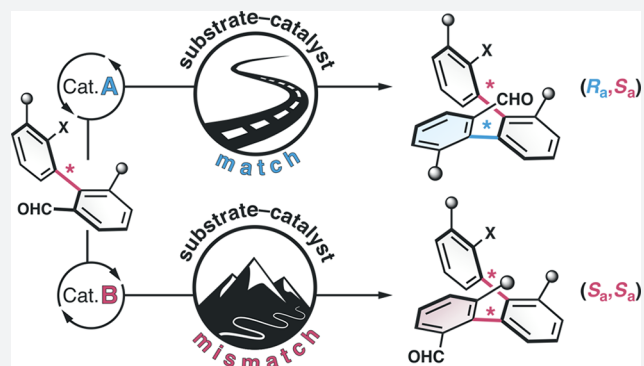
A defined relative orientation of groups in space is essential for the rational design of functional molecular systems. As structurally well-defined scaffolds, multiaxis systems offer a particularly broad range of topologies as compared to small, bridged, or linearly arranged compounds. Atropisomers with multiple configurationally stable axes would hence permit geometrical control over an extended and more characteristic molecular arrangement. However, for the configuration of each stereogenic axis to be individually addressed, a stereochemically versatile synthetic strategy is required,[1−3] where the choice of specific catalysts allow divergence of the diastereoselective reaction paths.

Seminal studies on diastereodivergent catalyst control over the stereocenter configuration underline the intricacies of the substrate−catalyst mismatch scenario, where selectivity for the unfavored product requires a particularly pronounced lowering of the activation energy (Scheme 1 top, cat. 2_B, TS_Bsubs vs TS_Bcat).[4−12] By implementing this consideration for the preparation of atropodiastereoisomers, stereodivergent syn- thesis of multiaxis systems under catalyst control would impose selectivity for an array of stereogenic axes, which induce a topologically unique structure (Scheme 1 bottom). We therefore envisaged that a catalyst-accelerated diastereoselective arene-forming aldol condensation[13,14] would provide discretely configured oligo-1,2-naphthylenes with multiple configuration- ally stable stereogenic axes. By catalyst variation, either the selectivity of a substrate-stereocontrolled reaction[15−26] could be increased, or more notably, the stereochemical course of the reaction could be inverted to provide otherwise inaccessible atropisomeric multiaxis systems with a characteristic molecular shape (substrate−catalyst mismatch case).

To evaluate the feasibility of the catalyst-controlled stereo- divergent synthesis of multiaxis atropisomers, we prepared a substrate with a previously defined stereogenic axis using our established procedure.[27] Addition of diaryl magnesium alkoxide reagent **1** to 1-bromonaphthalene-2-carbaldehyde (**2**) was followed by in situ double oxidation of diol (±)-**3** and an enantioselective arene-forming aldol condensation with (S)- pyrrolidinyl tetrazole catalyst **4** (99:1 er, Scheme 2). Building block **1** was subsequently added to the configurationally stable binaphthalene (S_a)-**5**[28,29] to give prerequisite precursor diol **6**.

Upon double-oxidation of **6** using IBX, the keto-aldehyde substrate was first converted to the ternaphthalene with two stereogenic axes under substrate stereocontrol (Table 1). Treatment with aqueous KOH thus revealed a 4:1 preference for (R_a,S_a)-**7** over (S_a,S_a)-**8** (entry 1).[30] We next investigated the stereodivergent synthesis of the atropisomeric two-axis system by evaluating the level of catalyst control of selected amine and ion-pairing catalysts under multiple reaction conditions.[31]

Intriguingly, (S)-pyrrolidinyl tetrazole catalyst **4** led to an inverted selectivity of 1:12 in favor of (S_a,S_a)-**8**, however, in low yield (entry 2, substrate-catalyst mismatched case). Upon optimization of the reaction conditions, chloroform, DMF, and aqueous citrate buffer as medium were found to provide (S_a,S_a)- **8** with increased selectivity and a significantly improved yield (75% over two steps, 32:1 dr, entries 3−5). We next corroborated that catalysts govern the stereochemical course of the reaction by using (R)-pyrrolidinyl tetrazole (ent-**4**) under identical conditions, affording the opposite diastereomer (R_a,S_a)-**7** with an atropodiastereoselectivity of 24:1 (entry 6, substrate−catalyst matched case). Moreover, the catalyst loading could be dramatically reduced by the use of ion-pairing
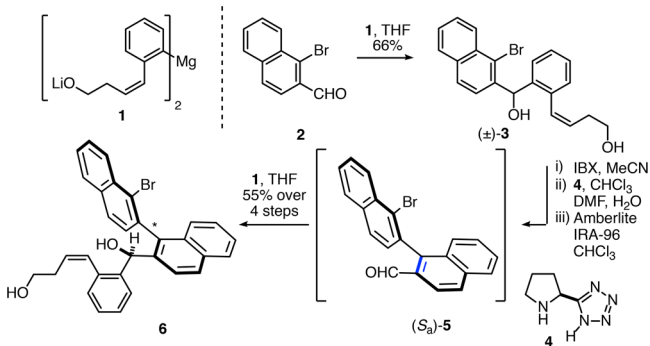
**Scheme 1. Catalyst-Controlled Diastereodivergent Synthesis[a]**
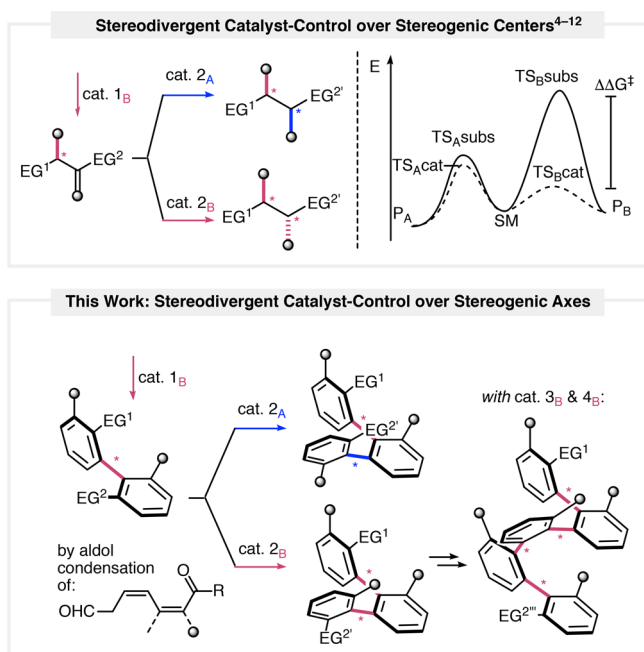
[a]Selectivity for the unfavored product (P_B) of a substrate-stereo-controlled reaction (TS_Asubs vs TS_Bsubs) requires a more pronounced lowering of the activation energy ($\Delta\Delta G^{\ddagger}$) under catalyst stereocontrol (TS_Acat vs TS_Bcat). EG: end group, SM: starting material.

Scheme 2. Substrate Synthesis

catalysts (aq KOH, entries 7−10). Whereas N-benzylcinchoninium chloride (**9**),[32−34] Maruoka catalyst **10**,[35−37] and Corey catalyst **11**[38] showed variable activity and selectivity, the cinchonidine-derived Lygo catalyst **12**[39,40] induced a high dr combined with a particularly high catalytic activity even if reduced to 1.0 mol % (entries 10−12).[31]

Having confirmed that the atropodivergent synthesis of a two-axis system enables the preparation of both atropodiastereoisomers under catalyst control, we became intrigued by the prospect of governing the configuration of an atropisomeric stereotriad. Building block addition to (S_a,S_a)-**8** (75%) and subsequent in situ oxidation of the corresponding diol expeditiously provided the corresponding keto-aldehyde, the substrate for the stereodivergent arene-forming aldol condensation in question. Interestingly, the level of substrate stereocontrol increased to 7:1 in favor of the homologous diastereomer (R_a,S_a,S_a)-**13** (Scheme 3). For this more pronounced substrate bias for the terminally (R_a)-configured

Table 1. In Situ Double Oxidation[a] and Optimization of the Catalyst-Controlled Stereodivergent Synthesis of an Atropisomeric Two-Axis System[b]
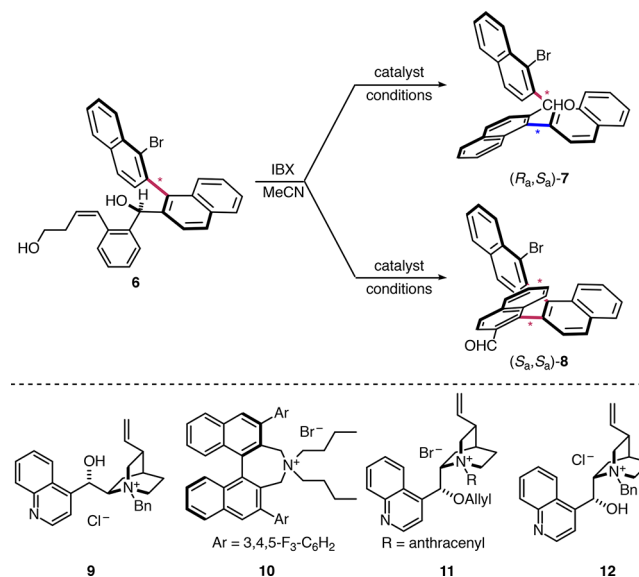

entry	catalyst (mol %)	solvent/additive	dr[c] (7:8)	yield[d]
1		CHCl$_3$/aq KOH	4:1	65%
2	**4** (40)	CHCl$_3$	1:12	13%
3	**4** (40)	DMF/H$_2$O	1:32	55%
4[e]	**4** (40)	CHCl$_3$/DMF/H$_2$O	1:24	54%
5[e,f]	**4** (40)	CHCl$_3$/DMF/aq buffer[g]	**1:32**	**75%**
6[e]	*ent*-**4** (40)	CHCl$_3$/DMF/aq buffer[g]	24:1	64%
7	**9** (10)	CHCl$_3$/aq KOH	8:1	54%
8	**10** (10)	CHCl$_3$/aq KOH	3.5:1	44%
9	**11** (10)	CHCl$_3$/aq KOH	3.5:1	18%
10	**12** (10)	CHCl$_3$/aq KOH	16:1	72%
11	**12** (5)	CHCl$_3$/aq KOH	16:1	70%
12	**12** (1)	CHCl$_3$/aq KOH	**16:1**	**69%**

[a]In situ double oxidation with 100 μmol substrate precursor **6** in MeCN and 300 μmol IBX at 60 °C for 4 h. [b]Stereodivergent aldol condensation with the specified catalyst and additive at RT for 24 h. [c]Ratio of (R_a,S_a)-**7**:(S_a,S_a)-**8** as determined by ^{1}H NMR of the crude reaction mixture. [d]Yield of isolated product over two steps. [e]Reaction time of 48 h. [f]Using 4.00 mmol substrate. [g]Sodium citrate buffer, pH 5.

atropisomer to be overcome, several catalysts and conditions were thoroughly examined.[31] Whereas primary and secondary amines proved inefficient, catalyst **12** was capable of forming helical (S_a,S_a,S_a)-**14** with a selectivity of 6:1, which was further improved to 8:1 at 0 °C (1.0 mol % **12**, aq KOH). The inversion of this considerable substrate preference with 1.0 mol % of **12** under otherwise identical conditions highlights the high efficiency of ion-pairing catalysts and indicates their particular utility for the substrate−catalyst mismatch scenario in the stereodivergent synthesis of multiaxis systems.

Encouraged by these results, we set out to investigate systems with four stereogenic axes individually addressed by catalyst stereocontrol. The required keto-aldehyde substrate poised for the arene-forming aldol condensation was accessible after a third building block addition to (S_a,S_a,S_a)-**14** (Scheme 4, 81%) and a subsequent in situ double oxidation. Under substrate stereocontrol, the additional repeating unit had a dramatic effect on the preference for quinquenaphthalene (R_a,S_a,S_a,S_a)-**15**, which was formed with a selectivity of 32:1. This increasingly prevalent bias however hampers the synthesis

Scheme 3. Stereodivergent Synthesis of an Atropisomeric Three-Axis System
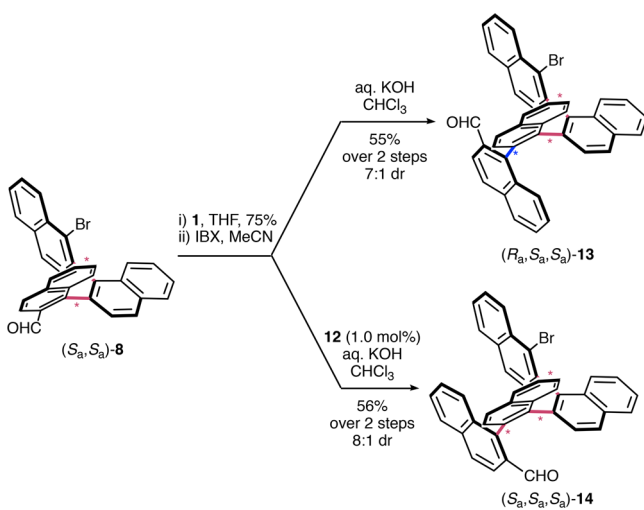
Scheme 4. Stereodivergent Synthesis of an Atropisomeric Four-Axis System
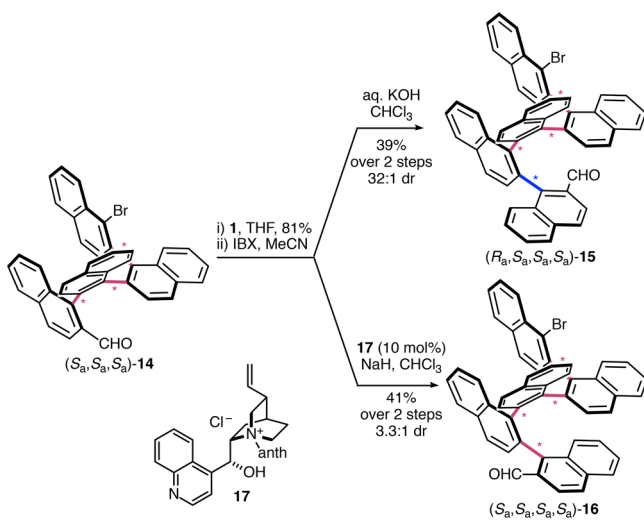
of (S_a,S_a,S_a,S_a)-**16**, as it requires diverging from a remarkably dominant reaction path. With N-benzylcinchonidinium chloride catalyst **12**, this preference was diminished but could not be overcome, and (R_a,S_a,S_a,S_a)-**15** remained the major product (1:3 dr, substrate–catalyst mismatch case). After meticulous experimentation using various prototypical catalysts and conditions,[31] anthracene-bearing catalyst **17** with an increased steric demand was identified to provide a 1:1 diastereoisomeric mixture. This suggests that activation energy parity was reached by compensation of the substrate bias for stereoisomer (R_a,S_a,S_a,S_a)-**15**. Gratifyingly, subsequent optimization revealed that a combination with sodium hydride allows the inversion of selectivity to give the desired (S_a,S_a,S_a,S_a)-**16** as a major product with a dr of 3.3:1.[31] An efficient catalytic system hence prevails even over a marked substrate bias (32:1 dr), enabling divergence of the atropodiastereoselectivity for the synthesis of a previously elusive stereotetrad.

Having both quinquenaphthalene diastereoisomers in hand, we next studied their characteristic structures by NMR spectroscopy. Large upfield shifts of the aldehyde protons (>1.0 ppm, 8.86 ppm) of the terminally (R_a)-configured

atropisomer **15** indicate a strong influence of the ring current from the second naphthalene unit to the aldehyde in proximity. Furthermore, substantial shifts of the aromatic protons (5.6 ppm) and clear NOE correlations between every third naphthalene unit of (S_a,S_a,S_a,S_a)-configured **16** were consistent with a compact helical secondary structure of the oligomers. These findings were further supported by the crystal structure of (R_a,S_a,S_a,S_a)-**15** (Figure 1)[41] with distances between the
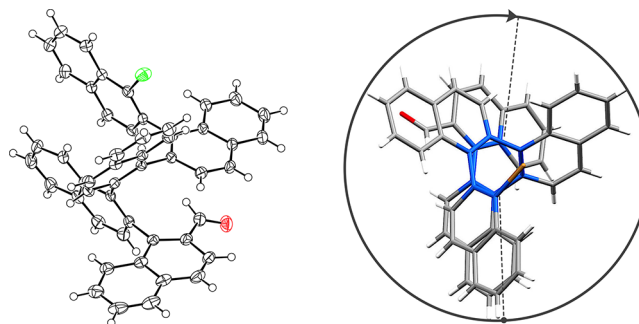

Figure 1. X-ray crystal structure of (R_a,S_a,S_a,S_a)-**15**. Thermal ellipsoids are drawn at the 50% probability level (left). View along the helix axis (right) with 1.53 turns (0.30 per unit) and an average torsional angle of 37° (average of 79° for four biaryls; average of 4° for five arenes).[15]

naphthalene moieties as small as 3.4 Å. The P-helical structure, particularly along the uniformly configured (S_a,S_a,S_a)-motif, is evident by the one and a half helix turns (a third turn per unit) and an average dihedral angle of 37° from alternating minimally distorted arene (5 × 4° in average) and their interstitial binaphthyl bonds (4 × 79° in average). These coil the configurationally stable ortho-arylene into a compact and distinctive geometry. We assume that only two conformers, resulting from the rotation about the arene-carbaldehyde bond, are accessible, whereas the oligo-1,2-naphthylene scaffold provides a configurationally entirely stable structure.

To evaluate the higher substrate bias with increasing oligomer length, we examined differences in their structures in solution. Interestingly, a comparison of the ring current effects of (S_a,S_a,S_a,S_a)-**16** with the shorter quaternaphthalene diastereoisomer (S_a,S_a,S_a)-**14** indicates that, with length, the helical arrangement is increasingly compact $(\Delta\delta_H(3_4 - \mathbf{14}_{4'''}) = 1.56$ ppm vs $\Delta\delta_H(3_4 - \mathbf{16}_{4''''}) = 1.91$ ppm), supporting the notion of Hartley that, in solution, the termini of ortho-arylenes are partially disordered.[42,43] Moreover, the lower substrate control observed in aromatic solvents is in agreement with partial disintegration of otherwise densely packed helices (2.7:1 dr (toluene) vs 7:1 dr (CHCl₃) for **13:14**).[31] To further evaluate the interplay of repulsive and attractive effects that influences the level of substrate stereocontrol, we investigated an arene substituent that diminishes aromatic interactions ((S_a)-**18**, triaryl amine end group, Scheme 5). Remarkably, with an electron-rich end group, the substrate bias is dramatically increased (19:1 dr for **19** vs 7:1 dr for **13**), whereas solvent effects remain minimal.[31] Although the addition of catalyst **12** has a comparable impact on the diastereoselectivity towards (S_a,S_a)-**20** (1:1.9 dr), attractive aromatic interactions likely facilitate the formation of the helical oligomers **14** and **16**. In combination, these results are in accordance with prevailing steric effects of the nucleophilic side chain with compact helices (for R_a) and opposing attractive interactions of the aromatic moieties (for S_a, helical).

Scheme 5. Effect of Substrate Substitution
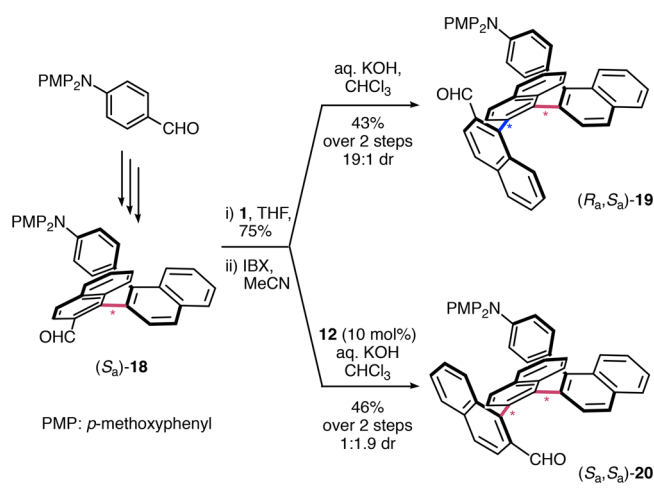
In conclusion, the configuration of multiaxis systems was individually addressed by catalyst-controlled atropodiadivergent synthesis. Up to four stereogenic axes were governed by amine and ion-pairing catalysts in arene-forming aldol condensations. Even in cases of a marked substrate−catalyst mismatch, otherwise inaccessible multiaxis atropisomers were efficiently prepared. To the best of our knowledge, this is the first example of a catalyst-controlled, stereodivergent synthesis of compounds with multiple stereogenic axes. The configuration of the rotationally restricted oligomers imposes a characteristic helical shape with a defined spatial arrangement. The stereodynamic behavior of the extended quinquenaphthalenes is reduced to a rotation about the terminal arene-carbaldehyde bond. The remarkable differences in substrate bias were attributed to opposing steric and aromatic interactions. Our current studies focus on the spatial positioning of pertinent groups by using structurally well-defined diastereoisomeric scaffolds.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.8b00204.

Experimental details and analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: christof.sparr@unibas.ch.

ORCID Ⓘ

Christof Sparr: 0000-0002-4213-0941

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(28) Compound (S_a)-**5** was found to decompose in a mixture of DMF and H_2O. The addition of $CHCl_3$ prevented the aldol dehydration step and hence also the decomposition. Dehydration was subsequently performed with Amberlite IRA-96 (polyamine resin).

(29) Heating an isolated, analytical sample of (S_a)-**5** to 180 °C did not lead to detectable racemization (neither neat nor in DMF).

(30) Product decomposition by the formation of dichlorocarbene was not observed under these conditions.

(31) See the Supporting Information for details.

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(40) Formation of product **7** or **8** was not observed without potassium hydroxide (with 10 mol % catalyst **12**).

(41) CCDC 1584599 (for compound (R_a,S_a)-**7**) and CCDC 1584600 (for compound (R_a,S_a,S_a,S_a)-**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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