Catalyst Control over Twofold and Higher-Order Stereogenicity by Atroposelective Arene Formation

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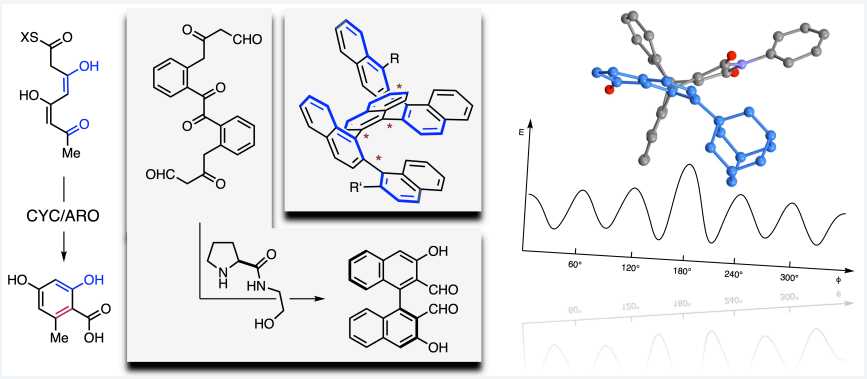


CONSPECTUS: Contradictory to the first intuitive impression that forging putatively flat aromatic rings evades stereoisomerism, a striking variety of atropisomeric compounds is conceivable by the formation of arenes, offering captivating avenues for catalyst-controlled stereoselective strategies. Since the assembled atropisomeric products that contain one or several rotationally restricted single bonds are characterized by especially well-defined molecular architectures, they are distinctly suitable for numerous pertinent applications. In view of the fascinating arene-forming aldol condensation pathways taking place in polyketide biosynthesis (CYC/ARO: cyclases/aromatases), the versatile small-molecule catalyzed aldol reaction appeared as an exceptionally appealing synthetic means to prepare various unexplored atropisomeric compounds in our efforts presented herein. In our initial studies, the use of secondary amine organocatalysts provided excellent selectivities in stereoselective arene-forming aldol condensations for a broad range of atropisomeric products, such as biaryls and rotationally restricted aromatic amides. In further analogy to polyketide biosynthesis, it was also conceivable that several aromatic rings are formed in catalytic cascade reactions. The use of small-molecule catalysts thereby enabled to transfer this concept to the conversion of unnatural and non-canonical polyketide substrates, thus giving access to atropisomers with particular value for synthetic applications. The versatility of the stereoselective aldol reactions with numerous catalytic activation modes further provided a strategy to individually control several stereogenic axes, similar to the various methodologies developed for controlling stereocenter configurations. By the use of iterative building block additions combined with catalyst-controlled aldol reactions to form the aromatic rings, stereodivergent pathways for catalyst–substrate matched and mismatched products were obtained. Besides secondary amines, cinchona alkaloid based quaternary ammonium salts thereby proved highly efficient in overcoming severe substrate bias. The obtained atropisomeric multiaxis systems, with all biaryl bonds suitably restricted in rotation even at high temperatures, are spatially distinctly defined. The helical secondary structure is therefore excellently suited for several captivating applications.

While previous catalyst-controlled stereoselective methods distinguish two stereoisomers for each stereogenic unit, catalyst control beyond the realms of this dualistic stereoisomerism remained unexplored. By selectively preparing Ōki atropisomers characterized by their sixfold stereogenicity in Rh-catalyzed [2+2+2]-cyclotrimerizations, one out of the six possible stereoisomers resulting from the restricted rotation of a single bond was shown to be catalytically addressable. Catalyst control over higher-order stereogenicity therefore further interconnects conformational analysis and stereoselective catalysis and offers captivating avenues to explore uncharted stereochemical space for creating a broad range of unprecedented molecular motifs.

▪ KEY REFERENCES

- Link, A.; Sparr, C. Organocatalytic Atroposelective Aldol Condensation: Synthesis of Axially Chiral Biaryls by Arene Formation. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461.[1] *In analogy to the aldol cyclizations taking place during the biosynthesis of aromatic polyketides, arene-forming aldol condensations to atropisomeric biaryls were developed. Small secondary amine catalysts provided excellent enantioselectivities and indicated the broad applicability of the concept.*
- Lotter, L.; Castrogiovanni, A.; Neuburger, M.; Sparr, C. Catalyst-Controlled Stereodivergent Synthesis of Atropisomeric Multiaxis Systems. *ACS Cent. Sci.* **2018**, *4*, 656–660.[2] *To suitably govern more than one stereogenic axis, stereodivergent catalyst control was established for atroposelective reactions. With one atropisomeric diastereomer formed preferentially due to substrate bias, efficient catalytic activation proved necessary to invert selectivity in the substrate–catalyst mismatched case.*

- Witzig, R. M.; Fäseke, V. C.; Häussinger, D., Sparr, C. Atroposelective synthesis of tetra-*ortho*-substituted biaryls by catalyst-controlled non-canonical polyketide cyclizations. *Nature Catal.* **2019**, *2*, 925–930.[3] *While enzymatic polyketide cyclizations are specific to natural oxygenation patterns, small-molecule catalysis allowed to convert substrates with non-canonical ketone arrangements. Their folding and a twofold stereoselective arene-forming aldol condensation thereby provided access to highly functionalized atropisomers with outstanding value for synthetic applications.*
- Wu, X.; Witzig, R. M.; Beaud, R.; Fischer, C.; Häussinger, D.; Sparr, C. Catalyst Control over Sixfold Stereogenicity. *Nature Catal.* **2021**, *4*, in print.[4] *In contrast to previous catalyst-controlled reactions that distinguish one out of two possible stereoisomers for any given stereogenic element in accord with the Le Bel–Van 't Hoff rule, catalyst-control over higher-order stereogenicity was conceived. The acquired stereoselectivity within six stereoisomers of Ōki atropisomers thereby further reunites the concepts of conformational analysis and stereoselective catalysis.*

1. INTRODUCTION

Stereoselective catalysis provides a basis for the synthesis of numerous pivotal products, such as bioactive pharmaceutical agents, natural products and compounds of great value in other areas of applications.[5-8] For instance, the advances in stereoselective synthesis have inspired and fueled the development of molecular machines[9] and functional materials.[10] A broad range of methods is focused on defining the configuration of one or more stereogenic centers by means of catalyst control.[11,12] While many of these methods are routinely used in organic chemistry and beyond, the control over other stereogenic elements is not yet fully established. Although great progress has been achieved in the stereoselective synthesis of biaryl atropisomers,[13,14] allenes,[15] and spiro compounds,[16,17] novel conceptual frameworks for distinct stereogenic elements, efficient preparative strategies and widespread applications may be awaited.

Most remarkably at the current stage, enantioselective biaryl coupling reactions,[18-22] the desymmetrization of stereodynamic biaryls,[23-27] dynamic kinetic resolutions and the *de novo* formation of aromatic rings[28,29] were established as pertinent catalytic approaches towards the enantioselective synthesis of biaryl atropisomers.[30] In this inspiring framework, we first disclosed the catalyst-controlled stereoselective arene-forming aldol condensation for the synthesis of binaphthyls.[1] The generality of the approach related to polyketide biosynthesis was thoroughly confirmed by the synthesis of atropisomeric aromatic amides[31] and the enantio- and diastereoselective synthesis of oligo-1,2-naphthylenes, comprising multiple stereogenic axes and a helical secondary structure.[2,32] Two general approaches emerged to set the configuration of multiple stereogenic units under catalyst control. The configurations of the stereogenic elements are defined either consecutively by a sequence of stereoselective reaction steps employing various catalysts,[33-35] or simultaneously in one step using a single catalyst[36] or a dual catalyst system.[37-39] Both approaches impose their challenges, particularly in the substrate–catalyst mismatch scenario where a preferred pathway resulting from interactions within the substrate has to be overcome. On the other hand, once control in the mismatched case is achieved, stereodivergence by the choice of catalyst provides a strategic route to the complete set of stereoisomers. Following the concept of iterative control over the configuration of stereogenic axes, we have applied arene-forming aldol condensations in the stereodivergent synthesis of oligo-1,2-naphthylenes giving rise to products with up to four defined atropisomeric axes.[2]

The elementary stereoisomerism of biaryl atropisomers is exemplified by tri- and tetra-*ortho*-substituted biaryls, such as compound **1**. The configuration of the stereogenic axis is commonly assigned as (S_a), denoting rapidly interconverting (+*sc*)- and (+*ac*)-conformers separated by a shallow rotational barrier (Figure 1).[40] In contrast, equilibration with enantiomeric (–*sc*)- and (–*ac*)- conformers via the (*sp*)- and (*ap*)- conformations (ϕ = 0° and 180° respectively) is kinetically restricted due to repulsive interactions between the four *ortho*-substituents. Since the rotational barrier is sufficiently large, the two enantiomers can be separated at usual temperatures. The related stereoisomerism of rapidly equilibrating conformers exemplified by *n*-butane (**2**) is often not considered, as the isomers cannot be separated under the typical conditions of an organic chemistry laboratory. Nonetheless, since experimental parameters can be gradually varied, only an arbitrary differentiation can be drawn, while the fundamental behavior remains the same. As with the four conformers of **1**, three conformers result by the rotation of

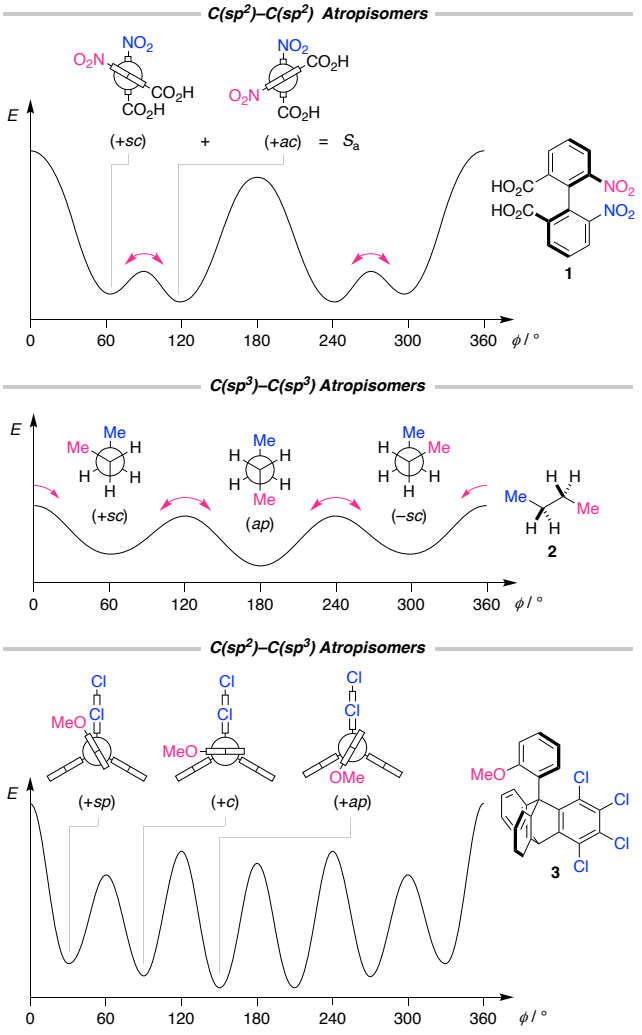


Figure 1. Qualitative rotational profile about C–C single bonds in biaryl atropisomers, *n*-butane and an Ōki atropisomer.

the middle bond of *n*-butane (**2**), two of which are enantiomers. While *n*-butane (**2**) and countless related compounds comprise stereogenic axes with threefold or higher stereogenicity, where irreducible stereogenic units give rise to three or more stereoisomers each, their bond rotational barriers are small[41] and the isomerism is typically not observed under synthetic conditions. In contrast, Ōki[42] and co-worker pioneered the conceptualization, preparation and isolation of unique rotational isomers with high configurational stabilty.[43] For instance, the bond rotational profile about the C(sp^2)–C(sp^3) bond of the Ōki atropisomer **3** consists of six minima corresponding to individual rotational isomers from a single stereogenic unit. In terms of rotational barriers, *n*-butane (**2**) and **3** differ strongly, and as a consequence, the large rotational barriers of **3** allow for the isolation and characterization of the six stereoisomers.[44]

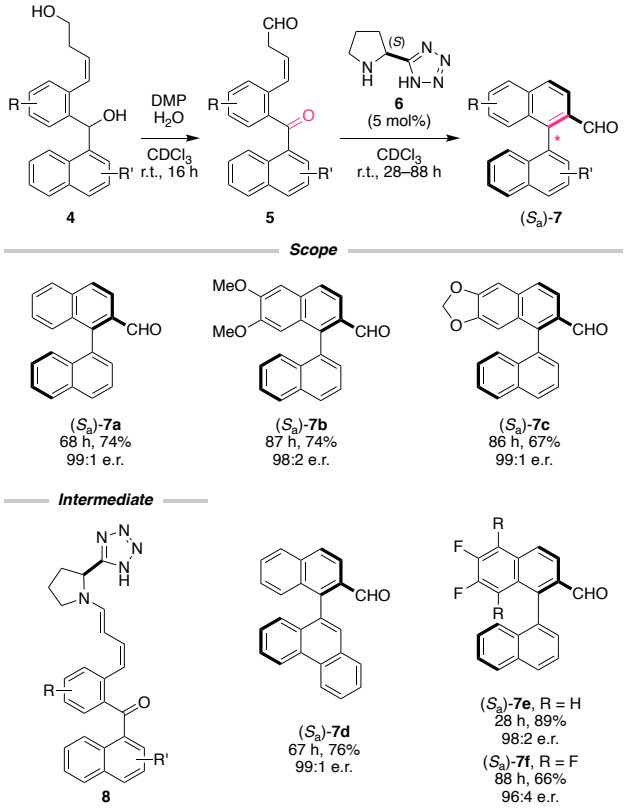
Owing to this intriguing stereoisomerism and the resulting stereochemical space which expands beyond the binary assignment of stereoisomers, our efforts were directed at the catalytic addressability of higher-order stereogenicity, controlling stereogenic elements that lead to more than a twofold differentiation of stereoisomers. We have recently disclosed catalyst control over sixfold stereogenicity by Rh-catalyzed [2+2+2]-cycloisomerizations,[4] while the stereoselective catalytic synthesis of other stereoisomers with higher-order stereogenicity is currently ongoing.

In this account, we outline our ongoing journey through the realms of atropisomeric molecules. Starting from aldol condensations that were inspired by polyketide biosynthesis, the atroposelective synthesis of binaphthyl systems with one stereogenic axis was established.[1] The methodology was unfolded to aromatic amides[31] and systems with up to four stereogenic axes.[2,32] Furthermore, we describe our efforts in the synthesis of molecules with higher-order stereogenicity.

2. CONTROL OVER A STEREOGENIC AXIS WITH TWOFOLD STEREOGENICITY

Taking the biosynthesis of aromatic polyketides into consideration, we first explored the synthesis of atropisomeric products by a catalytic arene-forming aldol condensation. Polyketide synthases (PKSs) catalyze the formation of aromatic compounds in bacteria, plants and fungi by intramolecular aldol condensation and aromatization/dehydrations of poly-β-carbonyl chains.[45,46] In our ongoing efforts to mimic these highly selective manipulations, we aim to access valuable scaffolds for medicine and organic synthesis by small-molecule catalysis.[47] Since the small-molecule catalyzed aldol reaction of poly-β-ketones is highly challenging due to their keto–enol tautomerism and the high reactivity of unreduced polyketide chains, structurally analogous dicarbonyl substrate **5** was investigated first (Scheme 1).[1] Because aldehyde **5** was found to be sufficiently stable in solution, it was generated *in situ* from **4**, which was accessed in three straightforward steps.

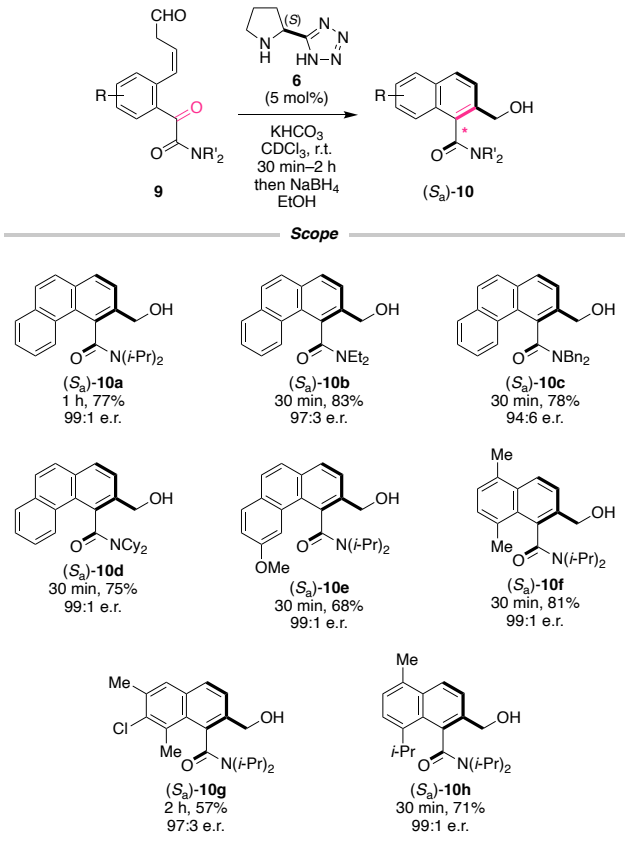
The wide range of applications of enantioselective catalytic aldol reactions, in which a secondary amine catalyst reliably activates a substrate by enamine formation under mild conditions,[5,14] convincingly demonstrates the efficacy and versatility of this activation mode. The irreversible formation of an aromatic system provides a large overall driving force for the transformation and was hence envisaged as additional virtue for this activation mode in atroposelective arene-formation reactions.



Scheme 1. Catalytic arene-forming aldol condensation providing enantioenriched binaphthyls.

Prior to the cyclization step, the aldehyde substrate is activated as dienamine **8** and the (*Z*)-configured double bond, together with the 1,2-disubstitution pattern of the aromatic ring, bring the nucleophilic α-carbon atom and the electrophilic keto group into close proximity. By stereoinduction from the C_1-symmetric catalyst, enantioenriched biaryls were obtained with the final configuration of the atropisomeric axis being fully established in the dehydration step. While the natural amino acid L-proline as catalyst provided good enantiocontrol, pyrrolidinyl-tetrazole **6**[48] enabled an exceptionally enantioselective and efficient reaction. Although electron-rich substrates required longer reaction times, the scope exploration revealed the generality of the arene-forming aldol condensation as both electron-poor and electron-rich substrates were obtained with high enantioselectivity.[1]

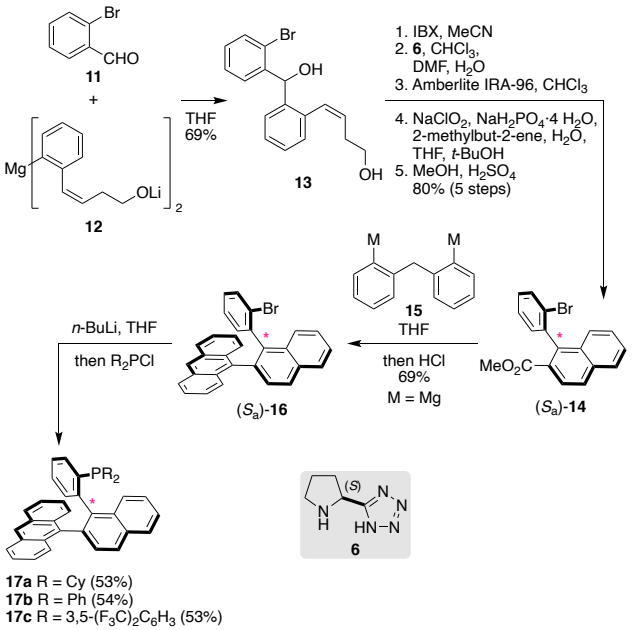
The broad applicability of the stereoselective arene-forming aldol condensation was further substantiated by the enantioselective preparation of atropisomeric aromatic amides with rotationally restricted Ar–CO bonds.[31] Interestingly, these intriguing atropisomers with potential applications in medicinal chemistry[49] and stereoselective synthesis,[50-52] were previously prepared in only few catalyst-controlled stereoselective processes.[53,54] Under catalytic control of **6**, the fast formation of the desired aromatic amides from **9** was observed (Scheme 2).[31] As some of the aromatic *ortho*-formyl compounds formed by the aldol condensation reaction racemized slowly at ambient or slightly elevated temperatures, the cyclization reaction was followed by an *in situ* reduction with $NaBH_4$ to provide *ortho*-hydroxymethyl-substituted aromatic amides **10** with higher configurational stability.[55]



Scheme 2. Atropisomeric aromatic amides accessible by enantioselective arene-forming aldol condensation reactions.

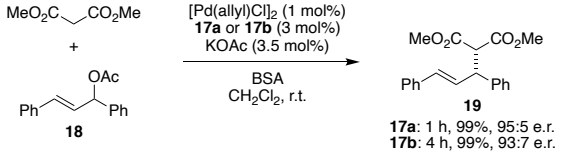
Since ligands with atropisomeric axes find widespread application in transition metal catalysis, it appeared predestined to employ the aldol condensation strategy to construct configurationally stable biaryls for their use as ligands in stereoselective catalysis. The atropisomeric JoyaPhos ligands, which were introduced lately, are configurationally and bench-stable teraryl monophosphines and were obtained in high enantiomeric purity by this strategy.[56]

The substrate for the arene-forming aldol condensation, the key step in the preparation of JoyaPhos ligands (Scheme 3), was prepared by IBX oxidation of **13**. The latter was expediently synthesized from 2-bromobenzaldehyde (**11**) and the mixed-metal organometallic building block **12**. The atropisomeric axis was established under catalyst control using tetrazole **6** followed by dehydration, which was assisted by the weakly basic ion exchange resin Amberlite IRA-96. The resulting biaryl was interconverted into atropisomeric biaryl ester (S_a)-**14** in two straightforward steps (80% yield over five steps). The direct ester-to-arene transformation of (S_a)-**14** with 1,5-bifunctional organomagnesium reagent **15**[57] provided the *ortho*-triaryl species (S_a)-**16** after elimination of water in the acidic work-up. (S_a)-**16** could be transformed effortlessly into the respective JoyaPhos ligand (S_a)-**17** by halogen–metal exchange and reaction with chlorophosphine R_2PCl (R = Cy, Ph, 3,5-$(F_3C)_2C_6H_3$). The X-ray structure analysis of gold(I) complexes Au(JoyaPhos)Cl revealed that the metal center is suitably accommodated in the cavity formed by the ligand scaffold.



Scheme 3. Synthesis of (S_a)-JoyaPhos ligands.

The efficacy of the JoyaPhos ligands (**17**) in catalytic transformations was demonstrated by the asymmetric allylic alkylation of **18** with dimethyl malonate (Scheme 4).[58] Both Cy_2JoyaPhos (**17a**) and Ph_2JoyaPhos (**17b**) provided **19** in high e.r. and excellent yield.[56] In addition, the JoyaPhos ligands were successfully employed in Au(I) and other Pd(0)-catalyzed reactions.[56]



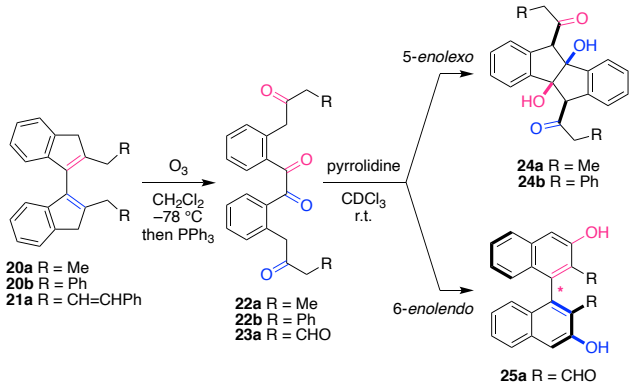
Scheme 4. Benchmarking JoyaPhos ligands in the Pd(0)-catalyzed asymmetric allylic alkylation. BSA = Bis(trimethylsilyl)acetamide.

While the synthetic aldol condensation reactions described above form one aromatic ring, PKSs often catalyze the simultaneous construction of multiple aromatic rings from polyketone substrates.[45,46] When subjecting a polyketone to aldol cyclization conditions, several chemo- and regioselectivity challenges arise from the multitude of reactive sites in the substrate and the intermediates. In PKSs, selectivity is typically guided by the stabilization of particular folding modes of a tautomeric form in the catalytic pocket of the enzyme, thus bringing activated reaction sites into close proximity. As mimicking these stabilizing effects for canonical polyketide cyclizations is yet an aim for small-molecule catalysis, other stabilization strategies, unnatural substrates and catalytic activation modes were envisaged.[59]

The configurationally stable binaphthyl scaffolds from our previous studies encouraged us to explore novel routes to aldol condensation substrates. We thereby aimed at constructing both aromatic rings by a twofold arene-forming aldol condensation from the non-canonical polyketide substrate **23**.[3] In the presence of a secondary amine catalyst, which would activate the

substrate as enamine, we envisaged that a 6-*enolendo-exo-trig* cyclization would provide binaphthyls **25**. Intriguingly, the substrates **22** and **23** were readily accessible by the two- or four-fold ozonolytic cleavage of biindenes **20** and **21** (Scheme 5).

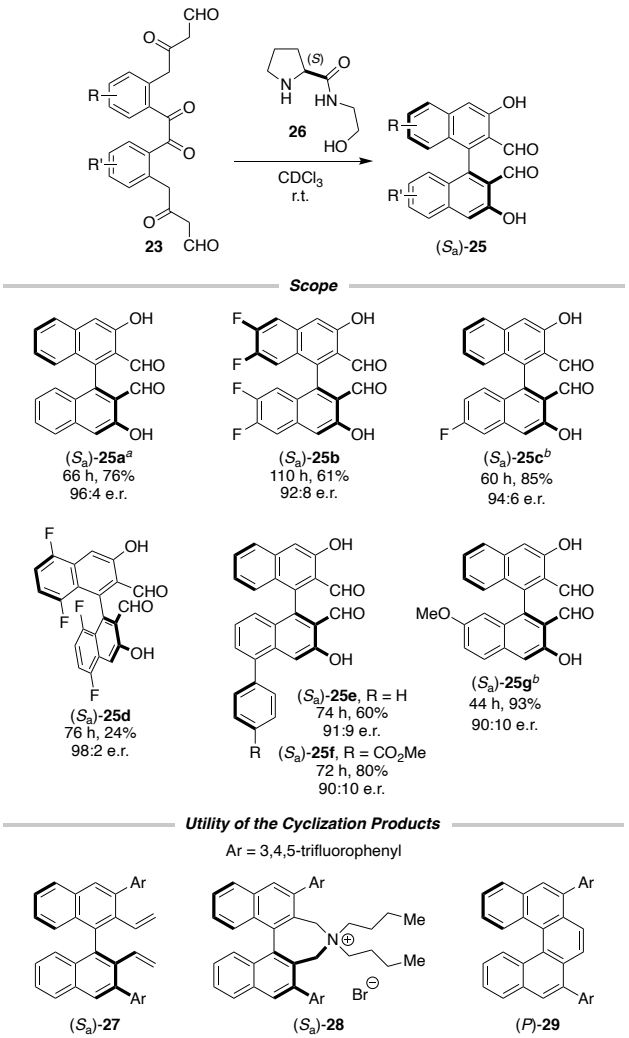
In order to explore the attainable folding modes of the non-canonical polyketones **22** and **23**, they were exposed to pyrrolidine catalysts and a strong effect of the substrate structure on the reaction outcome was encountered (Scheme 5). Starting with methyl-terminated substrate **22a**, its catalytic reaction provided exclusively hydropentalene **24a** as 5-*enolexo-exo-trig* cyclization product. The same reactivity was observed with phenyl-terminated polyketone **22b**, whereas terminal formyl groups provided the desired binaphthyl **25a** as only observable product.



Scheme 5. Twofold atroposelective aldol condensation to 6-*enolendo* vs. 5-*enolexo* cyclization products.

While L-proline and previously employed pyrrolidinyl-tetrazole catalyst **6** provided moderate yields of **25a** with moderate stereoselectivity, proline derivative **26** with a hydrogen-bond-donating side chain yielded **25a** in 82% yield with high enantioselectivity (95:5 e.r.). Whereas the introduction of other substituents at the aminoethanol side chain had only a minor impact on the invariably high enantioselectivity, a lower yield of binaphthyl **25a** was observed in comparison to catalyst **26** which can be prepared straightforwardly even on a large scale.

The scope of the non-canonical polyketide cyclization comprises both electron-poor and electron-rich substrates, and also sterically challenging substrates like **23d** can be transformed into the corresponding binaphthyls (Scheme 6). Since tetra-*ortho*-substituted biaryls are ideal materials for catalyst design, the utility of the binaphthyl scaffolds was demonstrated by preparing diene ligand **27** and Maruoka's ion pairing catalyst (IPC) **28**. Additionally, the enantioselective synthesis of configurationally stable [5]helicene **29** was feasible from the atropisomeric, non-canonical polyketide cyclization products.

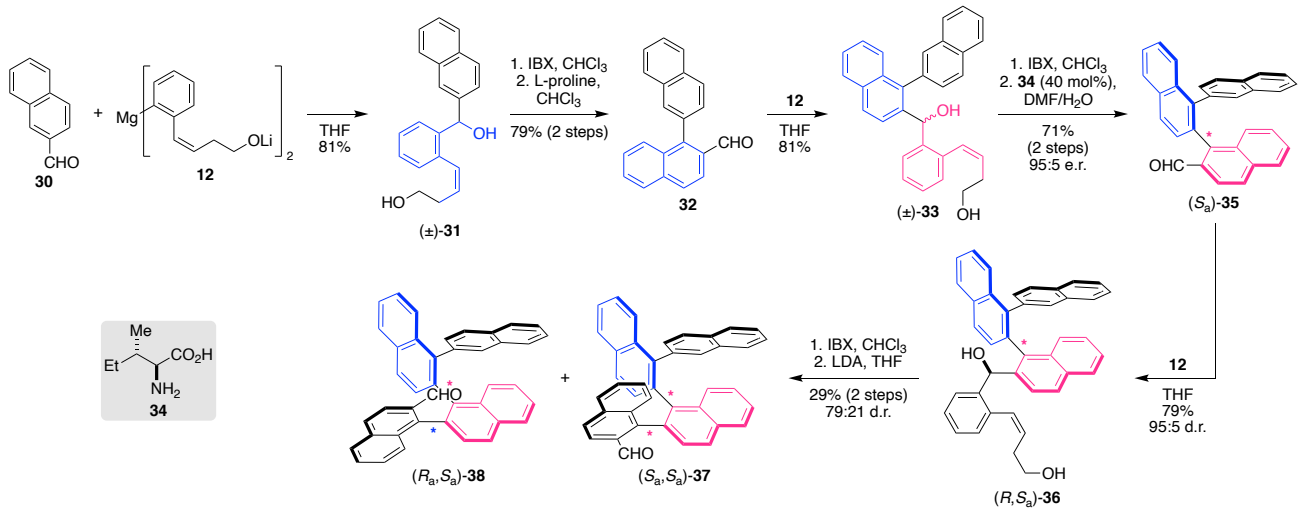


[a] Reaction performed on 1.00 mmol scale. [b] The dehydration was promoted by triflic acid.

Scheme 6. Enantioenriched binaphthyls accessible by twofold arene-forming aldol condensation.

3. ATROPISOMERIC MULTIAXIS SYSTEMS WITH TWOFOLD STEREOGENICITY

As predicted by the Le Bel–Van 't Hoff rule, molecules with stereotypical twofold stereogenic axes, such as C(sp^2)–C(sp^2) atropisomers (when neglecting shallow rotational barriers), may comprise 2^n stereoisomers with n denoting the number of stereogenic units. The overall topology of these molecules is thereby defined by the relative and absolute configurations of the stereogenic units. When the stereogenic axes in an atropisomeric multiaxis system are not aligned linearly, distinctive secondary structures are encountered.[60-64] If all axes have the same configuration, a helical secondary structure is obtained. These intriguing structural motifs comprise cavities, which could be used as active sites for asymmetric catalysis or molecular recognition, thus rendering their stereoselective preparation highly desirable.



Scheme 7. Stereoselective synthesis of oligo-1,2-naphthylenes by iterative arene-forming aldol condensations.

Atropisomeric1,2-oligoarylenes therefore emerged as particularly suitable scaffolds with multiple stereogenic axes. In order to obtain oligoarylenes with well-defined molecular architectures, the C(sp^2)–C(sp^2) bonds connecting the constitutional repeating units (CRU) must be configurationally stable, and in their synthesis, control over the configuration of all stereogenic axes needs to be gained.

Three major aspects motivated us to study our aldol condensation strategy for the sequential stereoselective synthesis of oligo-1,2-naphthylenes: The 1,1'-binaphthyls were obtained in excellent enantiomeric purity and displayed particularly high configurational stability; A large variety of catalysts was developed for stereoselective aldol condensation reactions, including amine and ion pairing organocatalysts, increasing the prospects of a stereodivergent synthesis of atropisomeric multiaxis systems, and; An iterative assembly process making use of a common organometallic building block for each CRU provides a straightforward approach to large systems comprising several CRUs. Conclusively, the individual control over the configuration of multiple stereogenic axes by different catalysts and thus over the secondary structure of the molecule was deemed feasible for this venture.

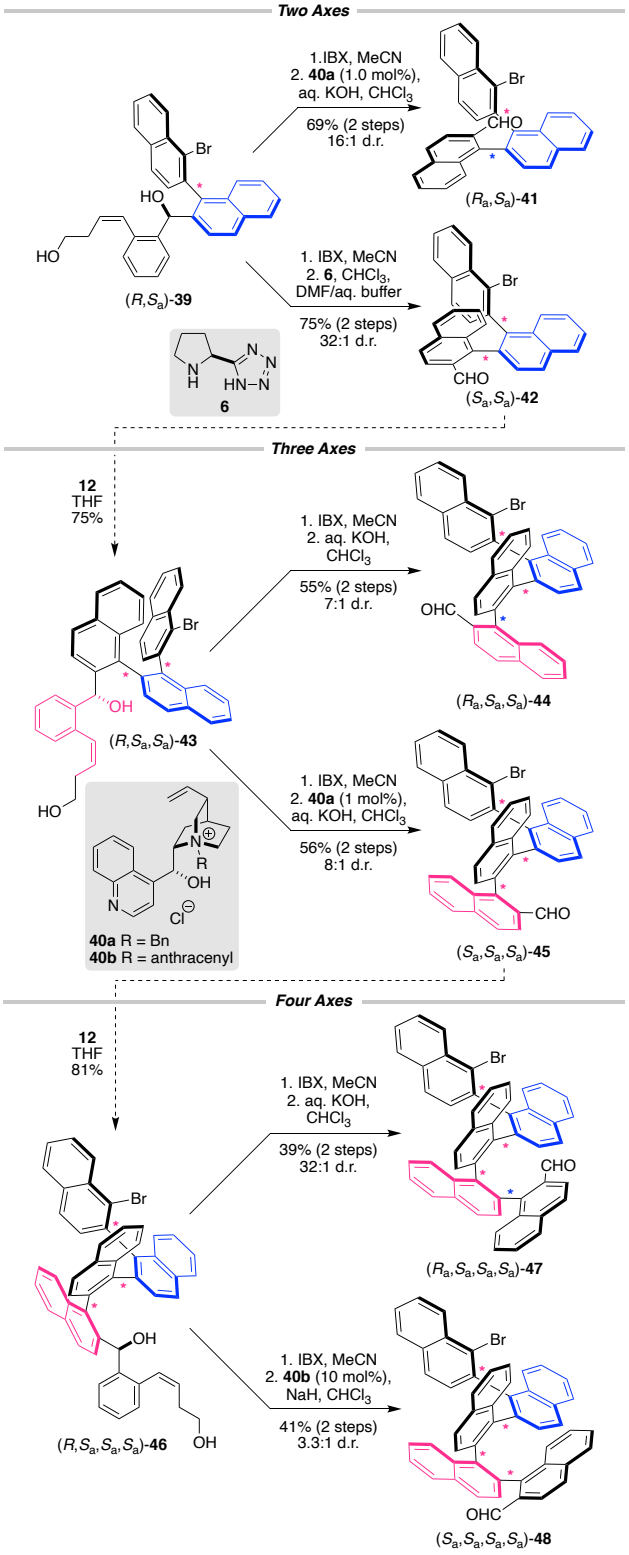
Before turning to large structures, the general viability of the intended route was examined by the synthesis of system **37**/**38**, which comprises two configurationally stable stereogenic axes (Scheme 7).[32] Starting from 2-naphthalenecarbaldehyde (**30**), which would become an end group of the desired oligo-1,2-naphthylenes, a sequence of the addition of organometallic building block **12**, *in situ* double oxidation with IBX and proline catalyzed aldol condensation was applied. By use of diaryl magnesium lithium alkoxide **12**, the protection of the alcohol function could be circumvented, increasing the overall efficiency.

Following the anticipated iterative assembly process, reagent **12** was added to intermediate **32**, and the resulting diol was oxidized with IBX. The oxidation product was fairly stable so that the exchange of solvent was possible before the aldol condensation. Pyrrolidinyl-tetrazole catalyst **6**, which was previously successful in the construction of single-axis C(sp^2)–C(sp^2) atropisomers,[1,31] provided high stereoselectivity but only low yield. Searching for alternate catalysts, several readily available canonical amino acids were tested, and L-isoleucine in a mixture of DMF and water was identified as optimal catalyst to obtain (S_a)-**35** in 71% yield with an e.r. of 95:5.

In order to confirm the concept of an iterative assembly, ternaphthylene (S_a)-**35** was extended with mixed-metal building block **12**. The addition proceeded smoothly and provided diol **36** with high diastereoselectivity. The stereocenter was oxidized in the subsequent step. Nevertheless, the diastereoselective addition of **12** indicates the highly defined spatial arrangement of the naphthalene units, creating a shielded environment around the carbaldehyde function. More importantly, the stereochemically distinct surrounding showed itself in the subsequently performed aldol condensation. Using LDA as base, (R_a,S_a)-**38** was obtained in a d.r. of 79:21 under substrate control.

These studies set the basis for our efforts to synthesize oligo-1,2-naphthylenes with stereodivergent catalyst control, to also provide products that are disfavored under substrate control.[2] In the substrate–catalyst match case, the selectivity of a diastereoselective reaction can be further increased by choosing a catalyst that lowers the activation barrier of the substrate's favored reaction path more strongly than of the disfavored one. On the other hand, inverting the diastereoselectivity requires the selection of a catalyst that lowers the activation barrier of the reaction path to the opposite diastereomer in the substrate–catalyst mismatch case. Gratifyingly, over the course of our studies, control over both the matched and the mismatched case could be achieved.

The sequential assembly of the oligo-1,2-naphthylene scaffold, which would ultimately lead to penta-1,2-napthylene **48**, was initiated from 1,2'-binaphthyl (R,S_a)-**39** containing one configurationally defined atropisomeric axis (Scheme 8). The substrate (R,S_a)-**39** was prepared as previously by using tetrazole catalyst **6** for the atroposelective arene-forming aldol condensation step. Double oxidation of (R,S_a)-**39** set the stage for the arene-forming aldol condensation, in which the configuration of the second stereogenic axis was controlled. In order to probe the level of substrate stereocontrol, the aldol condensation was promoted by aqueous KOH. This yielded (R_a,S_a)-**41** in a d.r. of 4:1, which could be enhanced to 16:1 by the addition of IPC **40a**.



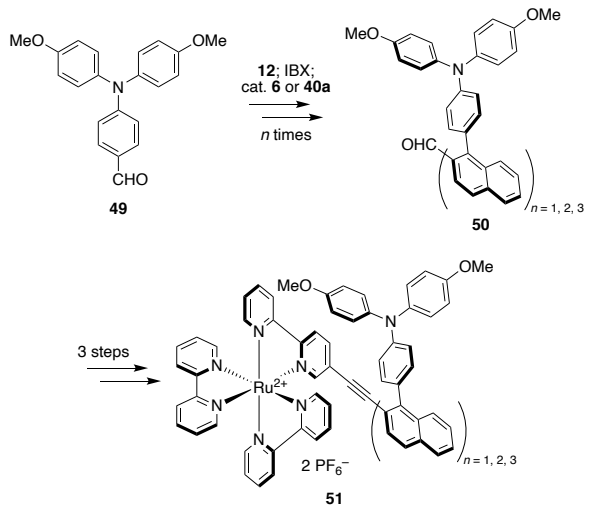
Scheme 8. Controlling diastereoselectivity in multiaxis atropisomeric oligonaphthylenes.

Setting out to achieve control over the substrate–catalyst mismatched case, a large variety of amine and ion pairing catalysts was investigated. Once again, pyrrolidinyl-tetrazole **6** was identified as suitable catalyst, which provided the substrate–catalyst mismatch-product (S_a,S_a)-**42** in 32:1 d.r. after reaction optimization. During the optimization process, a significant increase of both yield and diastereoselectivity could be affected by the use of a ternary solvent system comprising chloroform, DMF and aqueous sodium citrate buffer (pH 5). Notably, the enantiomeric form of the tetrazole catalyst (*ent*-**6**) also provided epimer (R_a,S_a)-**41** in 24:1 d.r. in 64% yield, illustrating its aptitude to divergently control the configuration of the second stereogenic axis.

Following the same sequence of building block addition and double oxidation with IBX as before, substrate (R,S_a,S_a)-**43**, which would yield triaxial system **44**/**45**, was prepared from (S_a,S_a)-**42**. IPC **40a** showed to be a good choice for controlling the mismatch scenario, which leads to (S_a,S_a,S_a)-**45**. Intriguingly, with a d.r. of 8:1, good stereoselectivity was observed. This is remarkable as substrate stereocontrol led to 7:1 d.r. for (R_a,S_a,S_a)-**44**, showing an even stronger bias than when controlling the second stereogenic axis.

The process of building block addition and oxidation was performed once more on the overall helical (S_a,S_a,S_a)-**45**. The KOH catalyzed aldol cyclization of the resulting dicarbonyl substrate yielded (R_a,S_a,S_a,S_a)-**47** in a very high d.r. of 32:1. Approaching the limits of catalyst control, the stereoselectivity was inverted in the substrate-catalyst mismatch-case by using IPC catalyst **40b**. However, due to the extraordinary strong substrate bias, the d.r. was impacted to provide 3.2:1 diastereoselectivity.

X-ray analysis of the oligo-1,2-naphthylene series revealed that the naphthalene moieties adopt an increasingly compact arrangement with growing size. This rationalizes the higher level of substrate stereocontrol in the aldol condensations of larger systems as the energetic difference between the diastereomeric transition states increases with the steric interactions within the substrate. Furthermore, the larger scaffolds become increasingly rigid and spatially defined, rendering atropisomeric multiaxis systems with their helical architectures as excellent scaffolds for relevant applications.



Scheme 9. Stereoselective synthesis of donor-bridge-acceptor dyads for electron transfer studies.

The helical secondary structure of the oligo-1,2-napthylenes and their stereodivergent preparation by the modular assembly provided a basis for a collaboration with the Wenger group (University of Basel) to study electron transfer processes.[65] A series of oligo-1,2-naphthylenes bearing a triarylamine electron donor and a $[Ru(bpy)_3]^{2+}$ electron acceptor at the termini of the oligomer was deemed suitable to differentiate pathways during

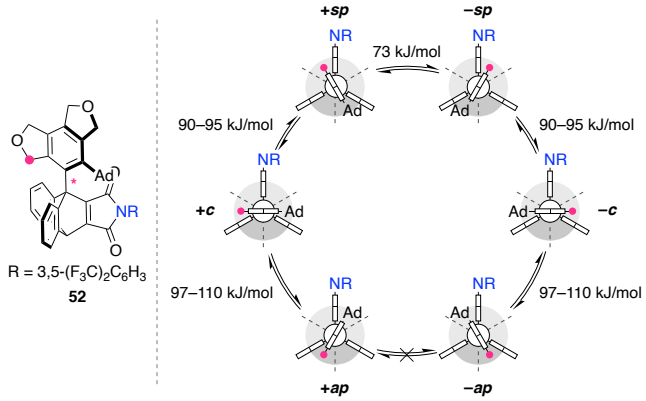
photoinduced electron transfer (PET).[66] In previous linear wire donor–bridge–acceptor dyads with an oligo-(*p*-phenylene) bridge, the rate of the PET was distinctly impacted by the distance between the donor and the acceptor moieties of the photochemical system.[67,68] In contrast, in corresponding oligo-1,2-naphthylenes **51**, which were synthesized by the sequential arene-forming aldol cyclizations followed by end-group functionalization (Scheme 9), an unusually weak dependence of the PET rate on the bridge length was encountered.[65] This intriguing observation was explained by the occurrence of alternate non-covalent tubular PET pathways involving shortcuts through the oligo-1,2-naphthylene backbone by non-covalent contacts.

4. CATALYST CONTROL OVER HIGHER-ORDER STEREOGENICITY

As outlined in the introduction of this account, stereochemical space includes stereogenic axes leading to more than two conformers per unit, but the conditions in organic synthesis often result in the rapid equilibration of these conformational isomers. In contrast, the Ōki atropisomers with rotationally restricted C(sp^2)–C(sp^3) bonds exemplify compounds with sixfold stereogenicity that are sufficiently configurationally stable even at elevated temperatures. These molecular scaffolds bear the potential to be used in various applications, for instance as precise angle-adjustment modules in molecular nanotechnology and in different form as bioactive compounds.[69,70] Nonetheless, catalyst control to select within >2 isomers per stereogenic unit to selectively navigate this vast stereochemical space remained undeveloped.

Our search for a suitable catalytic concept to provide configurationally stable products with sixfold stereogenicity was initiated with the interlocked Ōki atropisomer **52** (Scheme 11).[4] Its atropisomerism arises from the hindered rotation about the C(sp^2)–C(sp^3) single bond connecting the ethenoanthracenyl and the aryl moiety. By rotation about this bond, six conformers (three enantiomeric pairs) are separated by large rotational barriers. Studies on the thermal atropisomerization of compound **52** by NMR spectroscopy and HPLC on a chiral stationary phase allowed to determine energy barriers between 73 and 110 kJ/mol (Scheme 11). Intriguingly, direct racemization of the (*ap*)-conformers by surpassing their connecting saddle point does not take place. As a consequence, enantiomerization of the two (*ap*)-enantiomers is rather slow as it occurs through all other conformers. For catalyst control over sixfold stereogenicity, Rh-catalyzed [2+2+2]-cyclotrimerizations[28,29] of **53** to ethenoanthracene **55** with an increased interlocking and configurational stability was identified as viable approach. Gratifyingly, the investigation of various bisphosphine ligands, originally developed to differentiate stereogenic units for two isomeric states, revealed that the highly selective formation of the (+*ap*)-conformer is feasible with SPINOL-derived ligand **54**, providing the cyclization product in 75% yield and 93:7:0:0:0:0 stereoselectivity (+*ap*:–*ap*:+*sp*:–*sp*:+c:–*c*).

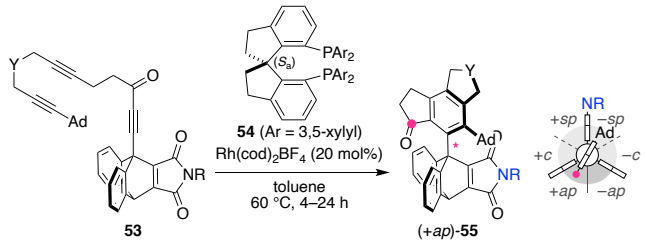
Fascinated by the feasibility of catalyst control over higher-order stereogenicity, the generality of the concept was investigated by the Rh-catalyzed cyclizations of different substrates (Table 1). Substrates with various *N*-aryl substituents in combination with an oxygen bridge provided similarly high stereoselectivity, and also benzyl *N*-substitution resulted in a stereoisomeric ratio of 95:5:0:0:0:0. Highest stereocontrol was achieved in electron-poor substrates. Furthermore, the effect of the bridging group Y on selectivity and reactivity was examined. Change from oxygen to *N*-tosyl thereby provided comparable high stereoselectivity.



Scheme 11. Atropisomerization mechanism in 52.

The unit with sixfold stereogenicity can be combined with an *N*-aryl substituent that leads to twofold stereogenicity from the restricted rotation about the N–Ar bond. In this case, the molecule can exist in the form of twelve stereoisomers. This was observed with an *ortho*-ethoxyphenyl substituted product, for which a thermodynamic d.r. of 2:1of equilibrating N–C(sp^2) atropisomers was obtained (entry 4).

Table 1. Catalyst control over sixfold stereogenicity.



	Y	R	Yield / %	Ratio of stereoisomers[a]
1	O	3,5-$(F_3C)_2C_6H_3$	75	**93**:7:0:0:0:0
2	O	4-Br-C_6H_4	83	**98**:2:0:0:0:0
3	O	4-Me-C_6H_4	80	**81**:19:0:0:0:0
4[b]	O	2-EtO-C_6H_4	79	**88**:12:0:0:0:0
5	O	Ph	74	**92**:8:0:0:0:0
6	O	3,4,5-$(MeO)_3C_6H_2$	71	**62**:38:0:0:0:0
7	O	Bn	76	**95**:5:0:0:0:0
8	NTs	3,5-$(F_3C)_2C_6H_3$	67	**90**:10:0:0:0:0
9	NTs	4-Br-C_6H_4	81	**75**:25:0:0:0:0
10	NTs	*n*-Pr	70	**70**:30:0:0:0:0
11	$C(CO_2Me)_2$	3,5-$(F_3C)_2C_6H_3$	81	**77**:23:0:0:0:0

[a] Given as (+*ap*):(–*ap*):(+*c*):(–*c*):(+*sp*):(–*sp*). [b] A 2:1 ratio of the atropisomers arising from restricted methoxyphenyl group rotation was observed.

Intriguingly, selective pathways to verify stereodivergent catalyst control were reached for four of the six stereoisomers with four different bisphosphine or *N*-heterocyclic carbene ligands.

5. CONCLUSIONS

In this account, we summarized our endeavors starting from polyketide biosynthesis inspired aldol reactions to catalytically control one or several stereogenic axes with twofold stereogenicity, which led us to our first steps to control higher-order stereogenicity. The atropisomers with rotationally restricted $C(sp^2)$–$C(sp^2)$ bonds were synthesized by an arene-forming aldol condensation using secondary amine catalysts to define the configuration of the stereogenic axis. By the capability of small-molecule catalysts to activate a broad range of unnatural substrates, also both aromatic rings of atropisomeric biaryls were forged by non-canonical polyketide cyclizations. The utility of the resulting binaphthyls was exemplified by their transformation into valuable ligands and catalysts. Atropisomeric multiaxis systems were prepared stereoselectively by an iterative assembly process and their configuration was controlled by stereodivergent catalysis. By exerting control over the substrate–catalyst mismatched case, overall helical oligo-1,2-naphthylenes with up to four stereogenic axes were obtained. The fascinating structural properties of these were utilized in ensuing applications such as electron transfer studies.

To expand catalytically addressable stereochemical space and to further interconnect the concepts of conformational analysis and stereoselective catalysis, we initiated a research program aiming at catalyst control over higher-order stereogenicity. A first cornerstone was established by the selective synthesis of atropisomers with sixfold stereogenicity in Rh-catalyzed [2+2+2]-cyclotrimerizations. While currently resorting on versatile catalysts originally developed to differentiate two stereoisomers per stereogenic unit, the possibility for extended stereodivergence highlights the exciting prospects of novel catalyst designs for controlling higher-order stereogenicity. Our current efforts focus on controlling stereogenic units with three- to fivefold stereogenicity and their enabling applications.

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Author Contributions

The manuscript was written by both authors.

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Notes

The authors declare no competing financial interest.

Biographies

Tanno A. Schmidt received his B.Sc. and M.Sc. in chemistry from the University of Tübingen (Germany). In 2019, he moved to Basel to conduct his doctoral studies with Prof. Christof Sparr working on the stereoselective synthesis of systems with fourfold stereogenicity under catalyst control.

Christof Sparr carried out his PhD work with Prof. Ryan Gilmour at the ETH Zurich. He subsequently joined the groups of Prof. Dieter Seebach and Prof. Steven V. Ley. After starting as habilitand mentored by Prof. Karl Gademann in 2013, Christof became Assistant Professor at the University of Basel in 2016 and was promoted to Associate Professor of Organic Chemistry in 2021.

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ABBREVIATIONS

CYC/ARO, cyclase/aromatase; CRU, constitutional repeating unit; DMP, Dess–Martin periodinane; IBX, 2-iodoxybenzoic acid; IPC, ion pairing catalyst; MSA, bis(trimethylsilyl)acetamide; PET, photoinduced electron transfer; PKS, polyketide synthase.

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