

Atropisomers

How to cite: *Angew. Chem. Int. Ed.* **2022**, *61*, e202202548

International Edition: doi.org/10.1002/anie.202202548

German Edition: doi.org/10.1002/ange.202202548

Synthesis of Atropisomeric Two-Axis Systems by the Catalyst-Controlled *syn*- and *anti*-Selective Arene-Forming Aldol Condensation

Daniel Moser and Christof Sparr*

Abstract: Simultaneous control over the configuration of multiple stereocenters is accomplished by numerous catalytic methods, providing a reliable basis for the synthesis of stereochemically complex targets in isomerically defined form. In contrast, addressing the configurations of multiple stereogenic axes with diastereodivergent catalyst control is thus far only possible by stepwise approaches. Herein we now describe that all four stereoisomers of atropisomeric two-axis systems are directly tractable by assembling a central aromatic unit of teraryls through an arene-forming aldol condensation. By using cinchona alkaloid-based ion-pairing catalysts, the four feasible reaction pathways are differentiated from identical substrates under defined basic conditions without preactivation, thus enabling complete stereodivergence with enantioselectivities of up to 99:1 e.r.

During gluconeogenesis, D-fructose 1,6-bisphosphate aldolase (FruA) exquisitely controls the configuration of two new stereocenters in the aldol addition of dihydroxyacetone phosphate (DHAP) to D-glyceraldehyde 3-phosphate (G3P), producing the *syn*-configured D-glucose precursor D-fructose 1,6-bisphosphate (F-1,6-BP, Figure 1A).^[1,2] Captivatingly, the diastereoselectivity is enzymatically diverted by D-tagatose 1,6-bisphosphate aldolase (TagA) so that identical substrates can also be transformed into the *anti*-configured product to encode the evolving carbohydrates with their specific functions.^[3] Similarly, L-lactaldehyde is converted either towards the *syn*-configured L-rhamnulose or the *anti*-configured L-fuculose in a direct aldol addition by differentiating the diastereomeric pathways (RhuA vs.

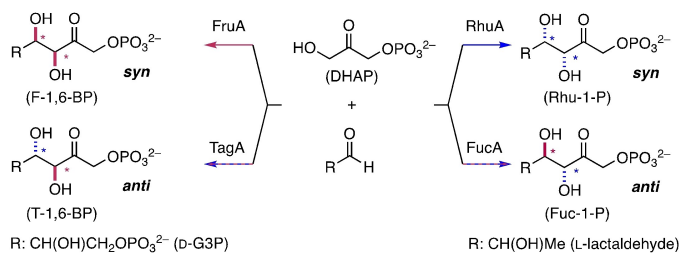
FucA).^[3] In analogy, Shibasaki developed a direct aldol addition to *anti*-configured products by using lanthanum binaphthoxide catalysts from substrates that were also converted to *syn*-aldols with chiral dizinc catalysts.^[4] While enantioselectivity is readily inverted with enantiomeric small molecule catalysts, diastereoselectivity is otherwise often dictated by the structure of the substrates, for instance in organocatalytic reactions. In their seminar work, List and MacMillan established *anti*-selective aldolizations of ketones and aldehydes,^[5,6] whereas only rare examples of diastereodivergent conversion of identical aldehydes were reported for primary or secondary amine catalysis, usually to convert prototypical *p*-nitrobenzaldehyde either to the *syn*- or the *anti*-aldol products (Figure 1B).^[7,8] Consequently, diastereoselectivity is usually secured indirectly by variation of the substrates^[9–12] or by preactivation related to the Mukaiyama aldol methodology.^[13] Notably, Denmark demonstrated that (*Z*)- or (*E*)- trichlorosilyl enolates are stereospecifically converted into the *syn*- or *anti*-aldol addition products, while enantioselectivities were controlled by the Lewis base catalysts.^[14] Nonetheless, the benefits of direct aldol methods are of significance,^[15] since catalyst-controlled enantio- and diastereoselectivity enables the conversion of identical substrates into all four possible stereoisomers within a single step.^[16] Considering the remarkable impact of the aldol reaction, the synthetically addressable stereochemical space is drastically expanded by direct catalytic enantio- and diastereodivergence to control different stereogenic units.

Juxtaposed to the ongoing method development to control stereocenter configuration by catalytic diastereoisomer selection, stereodivergent selectivity over the relative configuration of atropisomers by simultaneously establishing two defined stereogenic axes is yet an unsettled challenge. Analogous to aldol products with two stereocenters, atropisomeric two-axis systems exist as stable *syn*- and *anti*-configured diastereomers, such as in rotationally restricted, bis-tri-substituted *ortho*-teraryls (Figure 1C).^[17–20] Together with their enantiomers, these diastereomers represent topologically well-defined scaffolds with pertinent emerging applications.^[17–21] Our group previously developed an iterative strategy to prepare atropisomeric multi-axis systems by a stepwise catalyst-controlled stereodivergent approach.^[22,23] Encouraged by the efficient creation of stereochemical complexity by the simultaneous control over two stereocenters, we hence considered if the configuration of both stereogenic axis can be controlled simultaneously in a single catalytic step. The prospects of this notion were suitably

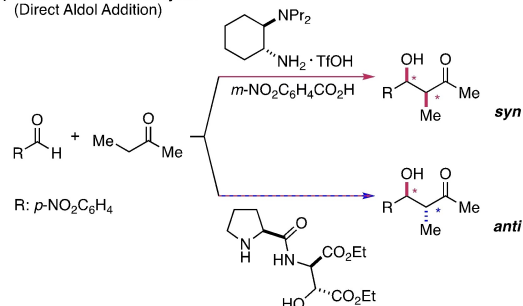
[*] D. Moser, Prof. Dr. C. Sparr
 Department of Chemistry, University of Basel
 St. Johannis-Ring 19, 4056 Basel (Switzerland)
 and
 NCCR Molecular Systems Engineering, BPR 1095
 Mattenstrasse 24a, 4058 Basel (Switzerland)
 E-mail: christof.sparr@unibas.ch
 Homepage: <http://sparr.chemie.unibas.ch>

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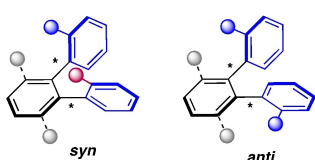
A) Carbohydrate Metabolism: Direct Aldol Reactions Stereocontrolled by Aldolases



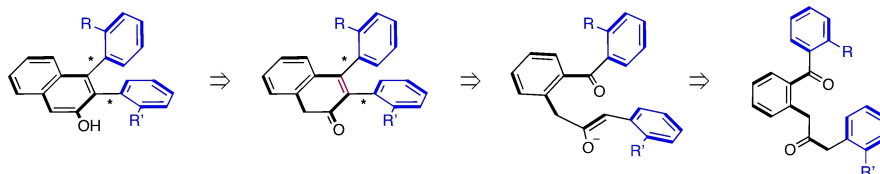
B) Small Molecule Catalysis (Direct Aldol Addition)



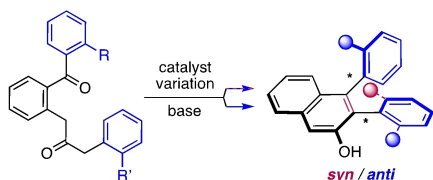
C) Diastereomeric Two-Axis Atropisomers



D) Polyketide Pattern Recognition in the Retrosynthetic Analysis



E) Atropisomeric Two-Axis Systems by the Direct Stereodivergent Aldol Condensation (this work)



F) Substrate Synthesis

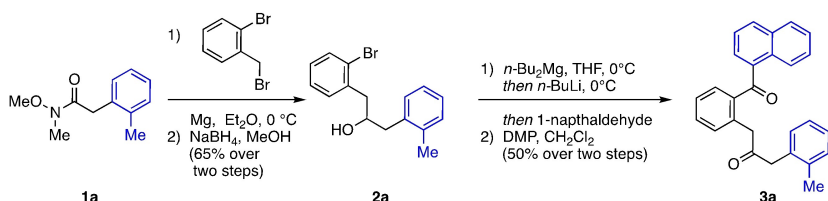


Figure 1. Background, conceptualization and substrate synthesis. FruA: D-fructose 1,6-bisphosphate aldolase; TagA: D-tagatose 1,6-bisphosphate aldolase; RhuA = L-rhamnulose 1-phosphate aldolase; FucA = L-fucose 1-phosphate aldolase. DMP = Dess–Martin periodinane.

underscored in the retrosynthetic analysis, in which the polyketide pattern of teraryls^[24] indicated that two *ortho* positioned stereogenic axes are established concurrently in the assembly of the inner β-naphthol ring from simple diketo substrates by means of an arene-forming aldol condensation (Figure 1D). If *syn*- and *anti*-configured products are selectively obtained with catalyst control, a stereodivergent approach would allow the programmed synthesis of all four feasible stereoisomers from the same substrate (Figure 1E). Herein, we report that this direct stereodivergent synthesis of atropisomeric two-axis systems is viable by simultaneously addressing both stereogenic units with organocatalytic stereocontrol, which allows to selectively access all conceivable atropisomers as major products.

We started our studies by preparing substrate **3a** with the readily available Weinreb *o*-tolylacetamide (**1a**) and the Grignard reagent from *o*-bromobenzyl bromide to give intermediate **2a** in 65% yield over two steps (Figure 1F). To circumvent protecting groups, a magnesium alkoxide was formed for an ensuing Br–Li exchange, which initiates a transmetalation^[25] to produce the Li-alkoxide Grignard reagent which was added to 1-naphthaldehyde. Upon final Dess–Martin oxidation, the diketo substrate **3a** was expeditiously prepared with 50% combined yield over both steps. With the exploratory substrate **3a** in hand, the feasibility of the envisioned aldol condensation was evaluated with catalytic amounts of *n*-Bu₄NBr, providing the atropisomeric two-axis teraryl in racemic form. We thereby noticed that an

ensuing acetylation facilitates purification and circumvents oxidation byproducts that are otherwise observed to a small extent. Notably, this procedure allowed the synthesis of a mixture of (±)-*syn*- and (±)-*anti*-teraryl **4a** with a 1:1 d.r. in an excellent yield of 96% (Figure 2A, entry 1). To establish the relative and absolute configuration of all stereoisomers, the enantiomers were isolated and assigned by X-ray crystallography with subsequent confirmation by CD spectroscopy, enabling a reliable identification and quantification of all four atropisomers by HPLC on a chiral stationary phase (see the Supporting Information for details).^[26] With the catalytic activity and the analytics of the teraryl formation established, we approached our primary objective of inducing catalyst-controlled stereoselectivity. Gratifyingly, when employing chiral cinchona-based ion-pairing catalyst **C1**,^[27] the *anti*-configured teraryl (*R_a,S_a*)-**4a** was obtained with >98% conversion, 3:1 d.r. and a promising enantioenrichment of 81:19 (entry 2). A combination of KOH and a strongly basic cationic resin (Amberlite IRA-400, quaternary ammonium Cl[−] form, polystyrene-DVB) was thereby identified as an optimal base for the catalytic aldol condensation to forge the central naphthol system. Moreover, Na₂SO₄ was found to improve stereoselectivity, likely by regulating the water content as indicated by control reactions with defined amounts of added water (see the Supporting Information). By using catalyst **C1** and its pseudoenantiomer **C2**, we next probed the effect of solvents, which confirmed that THF is the most suitable reaction

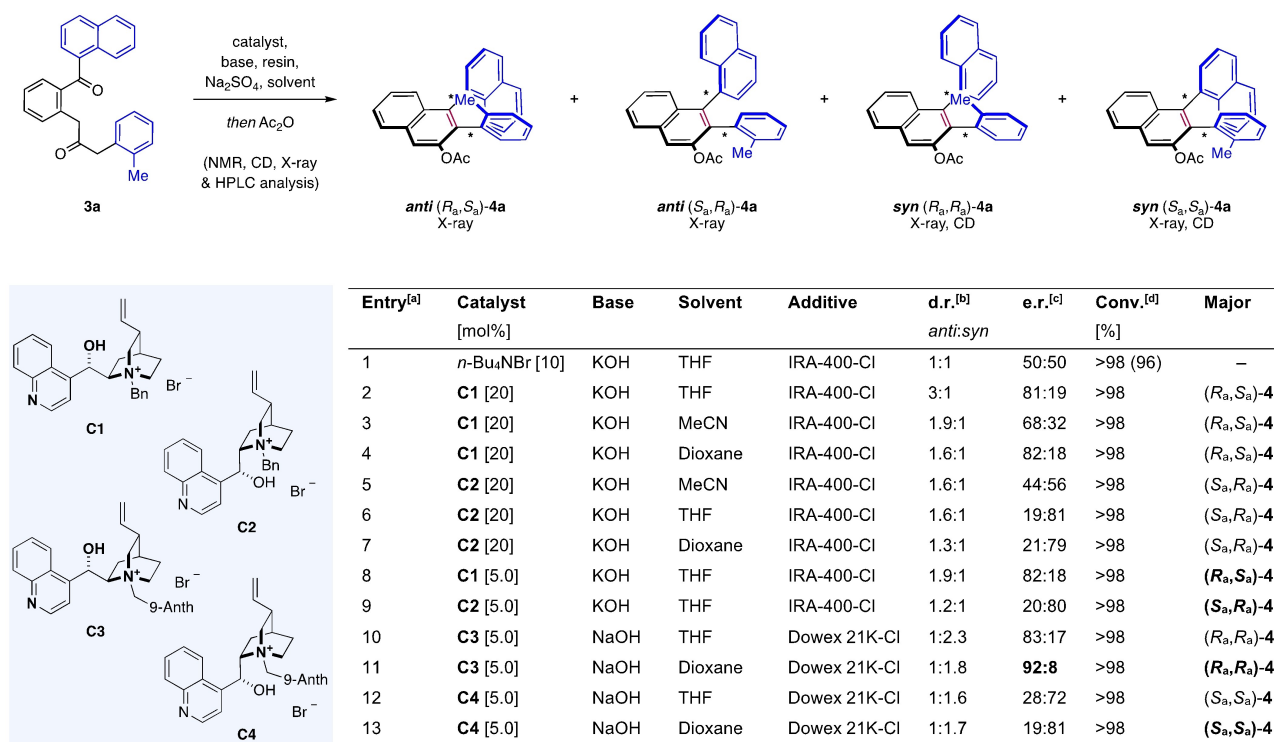
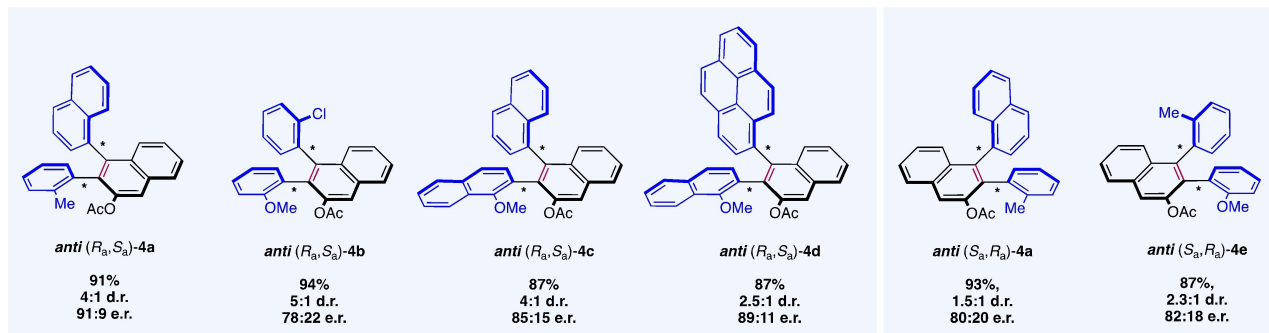
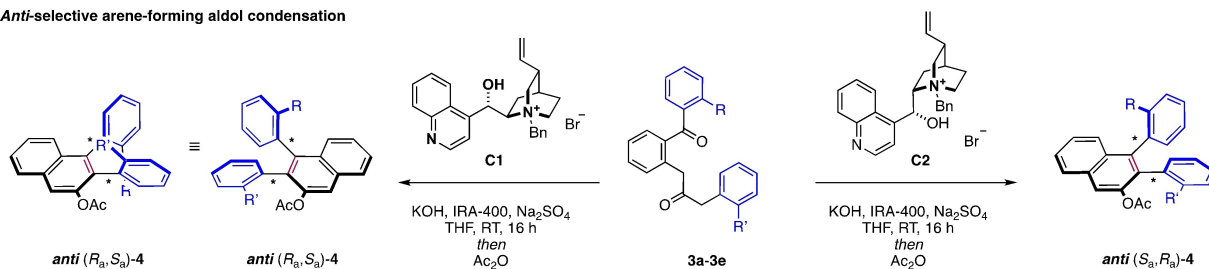
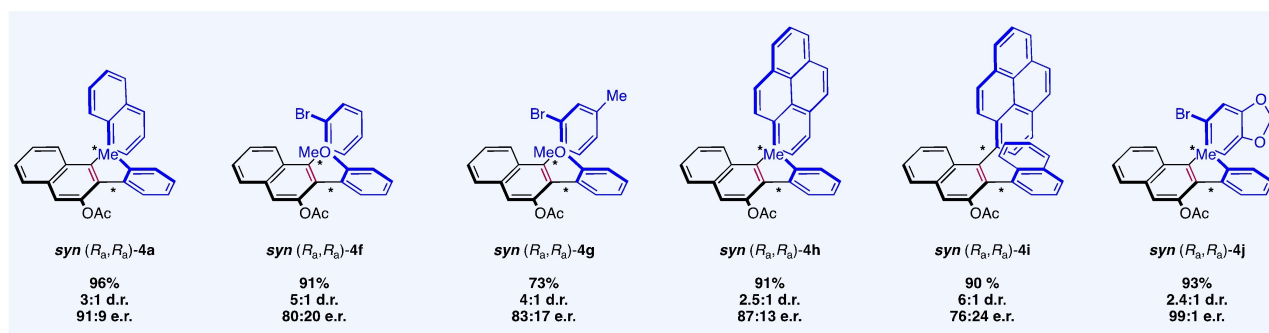
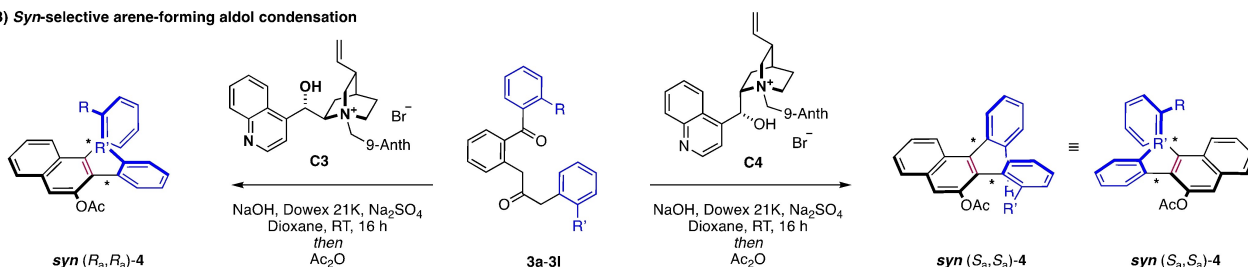


Figure 2. Synthesis of atropisomeric two-axis systems using *n*-Bu₄NBr for the racemic samples and optimization of the catalyst-controlled diastereodivergent arene-forming aldol condensation. [a] Conditions: 30.0 μmol **3a**, the specified amount of catalyst **C1–C4**, 60.0 μmol base, 90.0 mg additive, 135 mg Na₂SO₄ in 2.0 mL solvent under Ar at 22 °C for 16 hours, then 300 μmol Ac₂O, 22 °C, 30 min. [b] d.r. = *anti:syn* = [(*R_a*,*S_a*) + (*S_a*,*R_a*):[(*R_a*,*R_a*) + (*S_a*,*S_a1H NMR of the crude product and confirmed by HPLC on a chiral stationary phase. [c] e.r. of the major diastereomer determined by HPLC on a chiral stationary phase for the isolated product. [d] Isolated yield in brackets. CD = circular dichroism spectroscopy. 9-Anth = 9-anthracenyl.*

medium for both *anti*-configured enantiomers (entries 3–7). We were pleased to find that a similar enantioselectivity was also observed when the catalyst loading was reduced to 5.0 mol %, manifesting the efficiency of cinchona alkaloid-based ion pairing catalysis for the aldol condensation to form the atropisomeric two-axis systems (entries 8 and 9). With the conditions established for both *anti*-configured enantiomers, we tackled the main challenge of obtaining diastereodivergence in the direct aldol reactions to secure complete stereochemical addressability from an identical substrate. To differentiate the four possible pathways to each stereoisomer, selected catalysts, solvents, bases and ion exchange resins were explored (see the Supporting Information). Gratifyingly, the use of catalyst **C3** bearing an anthracenyl unit, dioxane as solvent and NaOH in combination with a strongly basic quaternary ammonium-functionalized resin (Dowex 21 K, Cl[−] form) revealed, that the diastereodivergent formation of *syn*-aldol products was feasible with 92:8 enantioselectivity (entries 10 and 11). Dioxane was the ideal solvent also with the pseudoenantiomeric catalyst **C4**, which allowed to invert enantioselectivity to give access to the fourth stereoisomer, thus establishing that all feasible isomers are obtained as major product within a single step from substrate **3a** without preactivation (entries 12 and 13).

After optimizing the four conditions of the enantio- and diastereodivergent catalytic arene-forming aldol condensation, we set out to explore the scope of the developed methodology (Figure 3). A variety of substrates was therefore tested for both the *anti*- and the *syn*-selective arene-forming aldol condensation, giving a distinct series of atropisomeric two-axis systems. The broad applicability of the *anti*-selective aldol condensation with catalyst **C1** was confirmed after increasing the reaction scale to 100 μmol and an isolated yield of 91 % was obtained (Figure 3A). Strikingly, we observed a scale-up effect in favor of higher selectivity and with catalyst **C1**, an isomeric enrichment with 4:1 d.r. and 91:9 e.r. was reached for the synthesis of (*R_a*,*S_a*)-**4a**. Notably, even a small chloro-substituent at the *ortho*-position ensured sufficient differentiation of the catalytic reaction with an increased diastereoselectivity for (*R_a*,*S_a*)-**4b** of 5:1. An *ortho*-methoxy group was also well tolerated, providing (*R_a*,*S_a*)-**4c** with higher enantioselectivity compared to (*R_a*,*S_a*)-**4b**. Remarkably, the method is also amenable for a substrate bearing a pyrene group and product (*R_a*,*S_a*)-**4d** was obtained with 89:11 e.r. The catalyst **C1** induced higher selectivity for the synthesis of (*S_a*,*R_a*)-**4a** when compared with the pseudoenantiomer **C2** (4:1 d.r., 91:9 e.r. vs. 1.5:1 d.r., 80:20 e.r.), whereas a similar efficiency was also observed for (*S_a*,*R_a*)-**4e**. The *syn*-configured product (*R_a*,*R_a*)-**4a** prepared on 100 μmol scale

A) *Anti*-selective arene-forming aldol condensationB) *Syn*-selective arene-forming aldol condensation

C) Variation of the functionalization procedure & derivatization

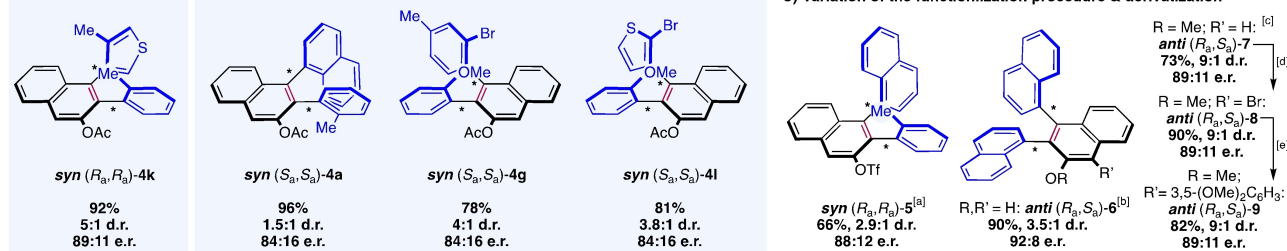


Figure 3. Scope of the *anti*- and *syn*-selective arene-forming aldol condensation. Conditions: 100 μmol 3a–l, 5.00 mol% C1 for (R_a, S_a)-, C2 for (S_a, R_a)-, C3 for (R_a, R_a)- and C4 for (S_a, S_a)-configured products, 200 μmol base as specified, 300 mg ion-exchange resin as specified, 450 mg Na_2SO_4 in 6.7 mL solvent as specified, under argon at 23 °C for 16 hours, then 1.00 mmol Ac_2O , 23 °C, 60 min. The d.r. was determined by ^1H NMR of the crude product and confirmed by HPLC on a chiral stationary phase. The e.r. was measured for the major diastereomer by HPLC on a chiral stationary phase for the isolated product. [a] Without Ac_2O , but with subsequent triflation of the naphthol using 300 μmol Trf_2O and 300 μmol Et_3N in CH_2Cl_2 . [b] Without Ac_2O . [c] Without Ac_2O , but with subsequent methylation of the naphthol using 500 μmol methyl iodide. Further enrichment of the *anti*-diastereomer before chromatography was observed due to its higher solubility. [d] With *N*-bromosuccinimide, DMF, 23 °C, 4 hours. [e] 3,5-(OMe)₂C₆H₃B(OH)₂, Pd(PPh₃)₄, K₂CO₃, THF, H₂O, 50 °C, 16 hours. 9-Anth = 9-anthracenyl. Tf = trifluoromethanesulfonyl.

using **C3** gave a 3:1 diastereoselectivity, the same 91:9 e.r. and an excellent isolated yield of 96% over both steps (Figure 3B). Likewise, the *syn*-selective aldol reactions were also found to be broadly applicable, allowing to prepare product (R_a,R_a)-**4f** bearing bromo and methoxy-groups with 5:1 d.r. Substrates with methyl groups at the *para*- and *ortho*-position gave (R_a,R_a)-**4g** and (R_a,R_a)-**4h** with somewhat higher enantioenrichment. As with the *anti*-selective aldol condensations, pyrene units were also compatible with the established conditions ((R_a,R_a)-**4h** and (R_a,R_a)-**4i**) and to our delight, the bromo-benzodioxol product (R_a,R_a)-**4j** was formed in 93% isolated yield and 99:1 enantioselectivity. Stereocontrol was even achieved with the pentatopic thiophene moiety in (R_a,R_a)-**4k**, which was obtained with a 4:1 d.r. in 92% yield by the aldol condensation after the ensuing acetylation step. Moreover, control for the opposite enantiomeric configurations was possible with catalyst **C4** and an isolated yield of 96% was afforded for (S_a,S_a)-**4a**, whereas a 4:1 d.r. was measured for (S_a,S_a)-**4g**. Furthermore, we also prepared the atropisomeric two-axis bromothiophene product (S_a,S_a)-**4l** and observed a similar isomeric distribution and a 81% yield.

The functionalization by in situ acetylation is readily replaced by a triflation with a comparable level of stereocontrol for (R_a,R_a)-**5** controlled by catalyst **C3** (3:1 d.r., 88:12 e.r., Figure 3C) as compared to (R_a,R_a)-**4a** (4:1 d.r., 91:9 e.r.). The direct aldolization products with large shielding groups were also isolable in high yield and selectivity without functionalization, as shown by the *anti*-configured (R_a,S_a)-**6**, which was smoothly obtained with **C1** in 90% yield, 3.5:1 d.r. and an e.r. of 92:8. Interestingly, a fourth substituent at the naphthalene core was readily introduced by a direct oxygen methylation and further derivatization by bromination combined with an ensuing Suzuki cross-coupling to give triarylated (R_a,S_a)-**9** without affecting the enantiopurity of the atropisomers. Furthermore, a notable configurational stability of the atropisomeric two-axis systems was measured by heating compound (R_a,R_a)-**4h**. No detectable racemization or epimerization occurred over four hours at 95°C, two additional hours at 115°C and even after further heating to 140°C for two more hours. The discrete topologies of the *cis*- and *trans*-configured atropisomers are thus stable over a large temperature range and consequently accessible by programmed synthesis by means of a direct diastereodivergent arene-forming aldol condensation. Moreover, by monitoring the reaction by ¹H NMR, we noticed similar reaction rates for the four stereoisomeric pathways and that the condensation products are directly formed without detectable aldol addition products or other noticeable intermediates. Besides establishing the feasibility of directly selecting all conceivable stereoisomers of configurationally stable atropisomeric two-axis systems by stereoselective organocatalysis, the practical diastereodivergent arene-forming aldol condensation enables a particularly efficient entry into stereochemically and topologically well-defined products with multiple stereogenic axes.

In conclusion, a diastereodivergent catalyst-controlled direct arene-forming aldol condensation to *anti*- and *syn*-

configured atropisomeric two-axis systems was developed. While aldolases selectively provide diastereodivergent pathways to control stereocenter configurations, the presented catalytic system allows the transformation of identical substrates into all possible atropisomers without preactivation. By using cinchona alkaloid-based ammonium salt catalysts, the viability of simultaneous control over two stereogenic axes was demonstrated by the efficient arene-forming aldol condensation of 1,5-diketones to provide various *ortho*-disubstituted β -naphthols. Furthermore, the mild reaction conditions and the broad functional group tolerance allowed the installation of various functionalities to synthesize structurally distinct molecular scaffolds with remarkable configurational stability. We thus anticipate that simultaneous diastereodivergent catalyst-control will allow strategic and expedient procedures to stereochemically complex atropisomers.

Acknowledgements

We gratefully acknowledge financial support from the Swiss National Science Foundation (155902 and 175746), the University of Basel and the NCCR Molecular Systems Engineering (182895). This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 101002471). We thank the Häussinger group for NMR support and Dr. Alessandro Prescimone for X-ray crystallography. Dr. Xingxing Wu and the other members of the Sparr group are acknowledged for fruitful discussions. Open access funding provided by the University of Basel. Open access funding provided by Universität Basel.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Aldolizations · Atropisomers · Cyclizations · Polyketides · Stereoselectivity

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Manuscript received: February 16, 2022

Accepted manuscript online: March 27, 2022

Version of record online: April 11, 2022