Bidirectional enantioselective synthesis of bis-benzofuran atropisomeric oligoarenes featuring two distal C–C stereogenic axes†

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We report the bidirectional enantiomeric synthesis of bis-benzofuran atropisomeric oligoarenes featuring two distal C–C stereogenic axes obtained by a two-fold central-to-axial chirality conversion upon oxidative aromatization. The key enantioenriched centrally chiral bis-dihydrobenzofuran precursors were synthesized via a bidirectional diastereo- and enantio-selective organocatalyzed domino reaction between simple achiral and easily accessible dihydroxylated aromatics and chloronitroalkenes. Moreover, the stereodivergent nature of the methodology was established by synthesizing both diastereomers of a non-symmetrically functionalized bis-axially chiral oligoarene.

Introduction

Oligoarenes are long pi-conjugated systems commonly used in a wide range of functional materials such as organic photovoltaics, dendrimers, and self-assembling polymers. They are also useful as precursors of more complex polyaromatic hydrocarbons and graphene nanoribbons. Over the past few decades, tremendous progress has been made in the development of protocols for the synthesis of oligoarenes and polyphenylenes. In this field, functionalized chiral oligoarenes bearing multiple stereogenic axes are particularly attractive for materials sciences, but their efficient enantioselective synthetic access remains a challenging task. In the few reported methods, proximal stereogenic axes are positioned on the same central aromatic core either on a 1,2- or on a 1,4-relationship as in teraryl or bis-styryl derivatives, respectively, or on a carbon–carbon double bond in a vicinal fashion (Scheme 1a). This is the case in the pioneering contributions of the groups of Tanaka and Shibata exploiting metal-catalyzed enantioselective [2 + 2 + 2] cycloadditions of achiral alkynes. More recently, Sparr’s and Zhou’s groups astutely combined enantioselective organocatalytic activation with chirality conversion to control oligo-1,2-naphthylenes or 2,3-diarylbzenoindoles, respectively. Complementarily, Yan and co-workers developed an enantioselective organocatalytic addition of arylsulfonates to an in situ generated vinylidene o-quinone methide for the synthesis of vicinal atropisomeric styrenes. Quite surprisingly, very little attention has been paid to the enantioselective synthesis of oligoarenes featuring two C–C stereogenic axes positioned on two distal aromatic rings also found in naturally occurring michellamines (Scheme 1b). In this field, Hayashi’s seminal contribution employed an enantioselective double Kumada

Scheme 1 Enantioselective synthesis of bis-atropisomeric oligoarenes featuring either proximal (a) or distal (b) stereogenic axes.
cross-coupling leading to symmetrically substituted ter-
naphthalene derivatives.\textsuperscript{13,14} This lack of methodologies for
the enantioselective synthesis of diversely functionalized
chiral oligoarenes, especially in the heteroaromatic series,
leaves space for a huge untapped potential. To fill this gap, we
report a new bidirectional enantioselective synthesis of bis-
benzofuran atropisomeric oligoarenes featuring two distal
C–C stereogenic axes.

Results and discussion

Our complementary bidirectional strategy starts from simple
achiral and easily accessible distal dihydroxy arene deriva-
tives 1 and chloronitroalkenes 2 (Scheme 2). Upon oxidative
aromatization of bis-dihydrobenzofurans 3, a double central-
to-axial chirality conversion would deliver the expected opti-
cally active S-shaped or E-shaped challenging atropisomeric
bis-benzofurans 4 featuring two distal stereogenic axes.
Moreover, the relatively large distance between both chiral
axes of these new functional polyaromatic sca
ffolds will forge
an interesting helically shaped molecular structure. The
success of this approach lies in the combination of a two-fold
diastereo- and enanto-selective organocatalyzed domino
heterocyclization with double oxidative aromatization
resulting in central-to-axial chirality conversion developed by
our group.\textsuperscript{15} Moreover, it is expected that these two successive
catalyst-controlled domino heterocyclizations would benefit
a chiral amplification based on the Horeau principle,\textsuperscript{16}
ensuring very high optical purities. Atropisomeric species
built on a five-membered ring are quite difficult to construct
in a stereoselective manner because of their lower configu-
trational stability.\textsuperscript{17} Consequently, the synthesis of molecules
displaying two fused benzofuran atropisomers would be even
more rewarding.

To validate these assumptions, we targeted first the synthesis
of bis-dihydrobenzofurans 3 based on the enantioselective
domino Friedel–Crafts-O-alkylation reaction between commer-
cially available 2,6-dihydroxynaphthalene (1a) and various
ortho-substituted \((Z)-(2\text{-chloro-2-nitroethenyl})benzenes\) (2).\textsuperscript{18}
The use of the chiral bifunctional squaramide-tertiary amine
organocatalyst \((R,R)-I\) in combination with a weak inorganic
base (K\textsubscript{2}HPO\textsubscript{4}) allowed the synthesis of the desired products 3a–
k, with good to excellent diastereoselectivity and an exceptional
level of enantiodiscrimination (96 to >99% ee), clearly indi-
cating the beneficial role of the Horeau chiral
amplification principle.

Importantly, the bidirectional domino bis-
heterocyclization proceeds smoothly twice under catalyst
control delivering mainly chiral diastereomers. However, in
some cases, we observed the formation of minor \textit{meso} dia-
stereomers (3c, 3e, 3h and 3i) as a result of a competitive
substrate-controlled reaction due to the bulkiness of the aryl
substituent.\textsuperscript{20} Many different functional groups are well
tolerated in this reaction such as electron-withdrawing substi-
tuents (3a–d, 3f, and 3j) and electron-donating ones
(3e, 3g, and 3h). The introduction of a 1-naphthalenyl group
in 3i was possible with excellent levels of diastereo-
and enanto-selectivities, albeit in lower yield (50%). The use of
anthracene-2,6-diol (1b) as the starting material gave the
desired fused bis-dihydrobenzofuran 3k in good yield as virtually a single enantiomer (>20 : 1, >99% ee). To further investigate the scope of the reaction, 2,3-dihydroxynaphthalene (1c) was used as the tetra-nucleophilic partner, leading to products 3l–n. In these cases, the closer proximity of the reactive sites results in a deeper impact of the aryl moiety in 2 toward the steric control of the reaction. A rather small methyl ester function gave very good enantioselectivity (95% ee) but a lower diastereoselectivity (3.8 : 1 dr) arguing for a mismatch situation between catalyst I and the monodihydrobenzofuran intermediate during the second heterocyclization to 3l. A decrease of the enantioselectivity was observed when the size of the aryl substituent increased (81% ee and 70% ee for products 3m and 3n with 2-Cl-C6H4 and 2-Br-C6H4, respectively). In these two cases, the enantiodiscrimination of the first step is not as efficient, possibly due to the proximity of the two OH functions, which could disturb the hydrogen-bond network in the transition state. Despite the poor diastereoselectivity in these last few cases, both diastereomers could be easily separated by chromatography on silica gel to be engaged in the following oxidative chirality conversion step. The absolute configuration of 3f was determined to be (S,S,S,S) by single crystal X-ray crystallographic analysis.22 On this basis and with the literature precedent,22 a plausible transition state is depicted in Scheme 4. The Michael acceptor 2f is activated by the squaramide moiety of cat. I while a hydrogen bond is established between the tertiary amine of cat. I and the hydroxy function of 1a. In this rigid hydrogen bond network, a Michael addition of 1a on the Si face of nitroalkene 2f would afford the adduct A. Then, a base promoted O-cyclization would give the trans-dihydrobenzofuran B. A second organocatalyzed domino Michael/O-cyclization sequence from B delivered the observed (S,S,S,S)-3f.

Next the investigation of the double central-to-axial chirality conversion was carried out. The use of manganese dioxide in toluene at 0 °C allowed the clean formation of the desired S-shaped bis-benzofuran atropisomers in the naphthalene series with very good yields and good to excellent enantiomeric excesses (Scheme 5, 4a–i: 91 to >99% ee). Bis-benzofuran 4j featuring a sterically congested o,o’-disubstituted aryl moiety is nevertheless obtained albeit with reduced yield (41%) and diastereoselectivity (3.6 : 1 dr) but still an acceptable 90% ee. In contrast, the oxidation of 3k with an anthracenyl central core gave the desired bis-benzofuran 4k in good yield and almost perfect diastereo- and enantioselectivities, positioning both stereogenic axes further away from each other. Finally, E-shaped bis-benzofuran atropisomers 4l–n with 2,3-dihydroxynaphthalene cores were obtained with similar efficiency and no erosion of the enantiomeric excess during the double conversion of chirality. The absolute configuration of product 4b was unambiguously determined to be (aS,aS) by X-ray diffraction techniques.23

Scheme 4 Proposed mechanism and transition state for the enantioselective synthesis of bis-dihydrobenzofurans 3.

Scheme 5 Scope of the double central-to-axial chirality conversion.19
accounting for a similar oxidation mechanism proposed in our previous work, following the Curtin–Hammett principle (Scheme 6). Hence, the two conformers $3\text{A}$ and $3\text{A}'$ are in equilibrium with a preference for $3\text{A}'$ where the sterically demanding group (blue ball) points outside from the furan subunit (see the X-ray result of $3\text{f}$, Scheme 3). This most stable conformation $3\text{A}'$ is apparently the least reactive under the oxidation conditions, because the hydride is shielded rendering the approach of the hydride acceptor ($\text{MnO}_2$) unfavorable. The result is the fast generation of the oxocarbenium ion intermediate $3\text{B}$. Subsequent deprotonation of the acidic hydrogen atom in $3\text{B}$ gives the enantioenriched $3\text{C}$ with efficient central-to-axial chirality conversion. Finally, iteration of this oxidative pathway from $3\text{C}$ gives the expected bis-furan atropisomer $4\text{A}$. The meso compound $4\text{B}$ could come from unfavorable stereoselection in either the first or the second oxidation step, while the minor enantiomer $4\text{C}$ could be obtained by two successive unfavorable stereoselections.

Based on the unique double catalyst-controlled bidirectionality of the process, we next target a stereodivergent approach leading to non-symmetrically functionalized S-shaped bis-atropisomeric oligoarenes (Scheme 7). This important feature has been addressed only once concerning molecules with multiple stereogenic axes.

Accordingly, we investigated the possibility of incorporating two different aryl groups and access to both diastereomers. First, the mono-functionalization of 2,6-dihydroxynaphthalene (1a) with 1 equiv. of chloronitroolefin $2\text{a}$ ($\text{Ar} = 2-\text{Cl-C}_6\text{H}_4$) and catalyst ($R,R$)-1 in a mixture of CHCl$_3$/THF (10 : 1) allowed the formation of the expected monodihydrobenzofuran $5\text{a}$ bearing a 2-chlorophenyl group in 55% yield and with excellent diastereo- and enantioselectivities (>20 : 1 dr, 96% ee). The second dihydrobenzofuran motif was constructed using the analogue $2\text{f}$ ($\text{Ar} = 2-\text{CO}_2\text{Me-C}_6\text{H}_4$). The same catalyst gave the $(2S,3S,7S,8R)$-$3\text{o}$ product in good yield (80%) and excellent stereoselectivity, while its enantiomer $(S,S)$-$1$ produced the diastereomer $(2R,3R,7S,8R)$-$3\text{o}$ in equally good yield (78%) and with perfect stereocontrol indicating absolutely no mismatch effect between $5\text{a}$ and the $(S,S)$-$1$ catalyst. Then the oxidation step was accomplished on both diastereomers of $3\text{o}$. Gratifyingly, the corresponding bis-benzofuran atropisomers $(aS,aS)$-$4\text{o}$ and $(aS,aR)$-$4\text{o}$ were obtained in good yields and excellent stereocontrol, with only a slight erosion of the diastereomeric ratio for $(aS,aS)$-$4\text{o}$ (17 : 1 dr).

![Scheme 6](image1.png)

**Scheme 6** Mechanism of oxidation.

![Scheme 7](image2.png)

**Scheme 7** Stereodivergent synthesis of S-shaped bis-atropisomeric oligoarenes.
Moreover, this non-symmetric synthesis shows the possibility of constructing original functionalized π-conjugated push–pull systems, with high potential in materials science.25

Finally, a step forward was taken by synthesizing more complex oligoarenes bearing two stereogenic axes even more distant form each other. This was possible starting from bis-naphthobenzofurandiol 1d and 1e. Compounds 3p and 3q were obtained in low yields (26% and 35%, see the ESI†) and still good to excellent enantioselectivity for the chiral diastereomer (88% and 98% ee) but with an unusual amount of the meso one (1: 1.4 and 3: 1 dr). Nevertheless, the chiral diastereomers could be separated by chromatography and engaged in the oxidative aromatization step (Scheme 8). Thus, the extended bis-benzofuran atropisomeric oligoarenes 4p and 4q were obtained in very good yields without erosion of the enantiomeric excess, accounting for a perfect double central-to-axial chirality conversion.

Conclusions

We have developed a unique bidirectional catalyst-controlled methodology allowing highly enantioselective access to hitherto unknown S- and E-shaped bis-benzofuran atropisomeric oligoarenes featuring two distal C–C stereogenic axes. The key feature lies in a successful double central-to-axial chirality conversion after organocatalyzed activation of simple and easily accessible achiral fused dihydroxyarenes and functionalized nitroolefins. This makes possible an unusual stereodivergent approach to these valuable new molecules featuring two different distal axes of chirality.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 For reviews, see: (a) C. Li, M. Liu, N. G. Pschirer, M. Baumgarten and K. Müllen, Chem. Rev., 2010, 110, 6817–6855; (b) Y. Lin, Y. Lia and X. Zhan, Chem. Soc. Rev., 2012, 41, 4245–4272; (c) G. Franc and A. K. Kakkar, Chem. Soc. Rev., 2010, 39, 1536–1544; (d) X. Zhang, T. Higashihara, M. Ueda and L. Wang, Polym. Chem., 2014, 5, 6121–6141.

2 (a) A. Narita, X.-Y. Wang, X. Feng and K. Müllen, Chem. Soc. Rev., 2015, 44, 6616–6643; (b) A. Bohnen, K.-H. Koch, W. Lüttke and K. Müllen, Angew. Chem., Int. Ed. Engl., 1990, 29, 525–527.

3 (a) S. J. Hein, D. Lehnerr, H. Arslan, F. J. Uribe-Romo and W. R. Dichtel, Acc. Chem. Res., 2017, 50, 2776–2788; (b) M. Arsenault, C. Wafer and J.-F. Morin, Molecules, 2015, 20, 9263–9294; (c) Q. Fan, J. M. Gottfried and J. Zhu, Acc. Chem. Res., 2015, 48, 2484–2494.

4 For diastereoselective strategies to optically active derivatives, see: (a) N.-X. Hu, S. Xie, Z. Popovic, B. Ong and A.-M. Hor, J. Am. Chem. Soc., 1999, 121, 5097–5098; (b) K. Takaishi, M. Kawamoto and K. Tsubaki, Org. Lett., 2010, 12, 1832–1835; (c) Q. Dherbassy, J.-P. Djukic, J. Wencel-Delord and F. Colobert, Angew. Chem., Int. Ed., 2018, 57, 4668–4672; (d) G. Beutner, R. Carraquillo, P. Geng, Y. Hsiao, E. C. Huang, J. Janey, K. Kati Molly, S. Kolotuchin, T. La Porte, A. Lee, P. Lobben, F. Lora-Gonzalez, B. Mack, B. Mudryk, Y. Qiu, X. Qian, A. Ramirez, T. M. Razler, T. Rosner, Z. Shi, E. Simmons, J. Stevens, J. Wang, C. Wei, S. R. Wisniewski and Y. Zhu, Org. Lett., 2018, 20, 3735–3740; (e) T. Yanagi, K. Nogi and H. Yoshimura, Synlett, 2011, DOI: 10.1055/S-0037-1611767.

5 (a) T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, J. Am. Chem. Soc., 2004, 126, 8382–8383; (b) T. Shibata and K. Tsukihara, Chem. Commun., 2005, 6017–6019; (c)
T. Shibata, K. Tsuchikama and M. Otsuka, Tetrahedron: Asymmetry, 2006, 17, 614–619; (d) K. Tanaka, T. Suda, K. Noguchi and M. Hirano, J. Org. Chem., 2007, 72, 2243–2246. For related molecules exhibiting both C-C and C-N vicinal axial chiralities, see: (e) O. Oppenheimer, R. P. Hsung, R. Figueroa and W. L. Johnson, Org. Lett., 2007, 9, 3969–3972.

6 (a) D. Lotter, M. Neuburger, M. Rickhaus, D. Häussinger and C. Sparr, Angew. Chem., Int. Ed., 2016, 55, 2920–2923; (b) D. Lotter, A. Castrogiovanni, M. Neuburger and C. Sparr, ACS Cent. Sci., 2018, 4, 656–660.

7 Y.-L. Hu, Z. Wang, H. Yang, J. Chen, Z.-B. Wu, Y. Lei and L. Zhou, Chem. Soc. Ed., 2019, 10, 6777–6784.

For other seminal studies, see: (a) J. A. Berson and E. Brown, J. Am. Chem. Soc., 1955, 77, 450–453; (b) T. R. Hollands, P. de Mayo, M. Nisbet and P. Crabbé, Can. J. Chem., 1965, 43, 3008–3017; (c) E. W. Warnhoff and S. V. Lopez, Tetrahedron Lett., 1967, 28, 2723–2727; (d) A. I. Meyers and D. G. Wettlaufer, J. Am. Chem. Soc., 1984, 106, 1135–1136.

For other examples of central-to-axial chirality conversion, see: (a) F. Guo, L. C. Konkol and R. J. Thomson, J. Am. Chem. Soc., 2011, 133, 18–20; (b) L. C. Konkol, F. Guo, A. A. Sarjeant and R. J. Thomson, Angew. Chem., Int. Ed., 2011, 50, 9931–9934; (c) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess and L. Kürti, J. Am. Chem. Soc., 2013, 135, 7414–7417; (d) Y.-H. Chen, D.-J. Cheng, J. Zhang, Y. Wang, X.-Y. Liu and B. Tan, J. Am. Chem. Soc., 2015, 137, 15062–15065; (e) J.-Z. Wang, J. Zhou, C. Xu, H. Sun, L. Kürti and Q.-L. Xu, J. Am. Chem. Soc., 2016, 138, 5202–5205; (f) M. Moliterno, R. Cari, A. Puglisi, A. Antenucci, C. Esperandio, E. Moretti, A. Di Sabato, R. Salvio and M. Bella, Angew. Chem., Int. Ed., 2016, 55, 6525–6529; (g) Y.-H. Chen, L.-W. Qi, F. Fang and B. Tan, Angew. Chem., Int. Ed., 2017, 56, 16308–16312; (h) H.-H. Zhang, C.-S. Wang, C. Li, G.-J. Mei, Y. Li and F. Shi, Angew. Chem., Int. Ed., 2017, 56, 116–121; (i) S. Maddox, G. A. Dawson, N. C. Rochester, A. B. Ayonon, C. E. Moore, A. L. Rheingold and J. L. Gustafson, ACS Catal., 2018, 8, 5443–5447; (j) L. W. Qi, J.-H. Mao, J. Zhang and B. Tan, Nat. Chem., 2018, 10, 54–64.

10 (a) Y. Tan, S. Jia, F. Hu, Y. Liu, L. Peng, D. Li and H. Yan, J. Am. Chem. Soc., 2018, 140, 16893–16898; (b) During the proof reading of this article, Yan and co-workers reported the enantioselective synthesis of compounds bearing both helical and axial stereogenic elements: S. Jia, S. Li, Y. Liu, W. Qin and H. Yan, Angew. Chem., Int. Ed., 2019, DOI: 10.1002/anie.201909214.

11 J. Rodríguez and D. Bonne, Chem. Commun., 2019, 55, 11168–11170.

12 G. Brinngman, R. Götz, S. Harmsen, J. Holenz and R. Walter, Liebig’s Ann., 1996, 2045–2058.

13 T. Hayashi, K. Hayashizaki and Y. Ito, Tetrahedron Lett., 1989, 30, 215–218.

14 A non-stereoselective double Suzuki reaction has also been employed for the total synthesis of naturally occurring racemic michelamines: (a) G. Brinngman, R. Götz, P. A. Keller, R. Walter, M. R. Boyd, F. Lang, A. Garcia, J. J. Walsh, I. Telliti, K. V. Bhaskar and T. R. Kelly, J. Org. Chem., 1998, 63, 1090–1097; (b) P. D. Hobbs, V. U. Upender and M. I. Dawson, Synlett, 1997, 965–967.

15 (a) O. Quinonero, M. Jean, N. Vanthuyne, C. Roussel, D. Bonne, T. Constantieux, C. Bressy, X. Bugaut and J. Rodríguez, Angew. Chem., Int. Ed., 2016, 55, 1401–1405; (b) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne and J. Rodríguez, J. Am. Chem. Soc., 2017, 139, 2140–2143.

16 J. P. Vigneron, M. Dhaenens and A. Horeau, Tetrahedron, 1973, 29, 1055–1059. For a recent review, see: A. M. Harned, Tetrahedron, 2018, 74, 3797–3841.

17 (a) D. Bonne and J. Rodríguez, Chem. Commun., 2017, 53, 12385–12393; (b) D. Bonne and J. Rodríguez, Eur. J. Org. Chem., 2018, 2417–2431. For recent contributions, see: (c) S.-C. Zheng, Q. Wang and J. Zhu, Angew. Chem., Int. Ed., 2019, 58, 1494–1498; (d) Y. Kwon, J. Li, J. P. Reid, J. M. Crawford, R. Jacob, M. S. Sigman, F. D. Toste and S. J. Miller, J. Am. Chem. Soc., 2019, 141, 6698–6705; (e) H. Li, X. Yan, J. Zhang, W. Guo, J. Jiang and J. Wang, Angew. Chem., Int. Ed., 2019, 58, 6732–6736; (f) X.-L. He, H.-R. Zhao, X. Song, B. Jiang, W. Du and Y.-C. Chen, ACS Catal., 2019, 9, 4374–4381.

18 (a) C. Jarava-Barrera, F. Esteban, C. Navarro-Ranninger, A. Parra and J. Alemán, Chem. Commun., 2013, 49, 2001–2003; (b) M. Rueping, A. Parra, U. Uria, F. Besselièvre and E. Merino, Org. Lett., 2010, 12, 5680–5683; (c) D. Becerra, W. Raimondi, D. Dauzonne, T. Constantieux, D. Bonne and J. Rodríguez, Synthesis, 2017, 49, 195–201; (d) For the synthesis of achiral furans from (Z)-(2-halo-2-nitroethenyl) benzenes, see: W. Raimondi, D. Dauzonne, T. Constantieux, D. Bonne and J. Rodríguez, Eur. J. Org. Chem., 2012, 6119–6123.

19 Yield of the isolated product. The diastereoselectivity was determined by 1H NMR spectroscopy of the crude reaction mixture. The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

20 See the ESL.

21 (a) X.-L. Zhang, K.-X. Feng, A.-B. Xia, Y.-Y. Zheng, C. Li, X.-H. Du and D.-Q. Xu, Eur. J. Org. Chem., 2018, 2918–2925; (b) J. Feng, L. Lin, K. Yu, X. Liu and X. Feng, Adv. Synth. Catal., 2015, 357, 1305–1310.

22 CCDC 1923303 (3f) contains the supplementary crystallographic data for this paper.

23 CCDC 1921425 (4b) contains the supplementary crystallographic data for this paper.

24 S. Krautwald and E. M. Carreira, J. Am. Chem. Soc., 2017, 139, 5627–5639.

25 (a) F. Bures, RSC Adv., 2014, 4, 58826–58851; (b) M. Kivala and F. Diederich, Acc. Chem. Res., 2009, 42, 235–248.