Noncanonical Catalyst-Controlled Polyketide Cyclisation: Atroposelective Synthesis of Tetra-*ortho*-Substituted Biaryls

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The cyclisation of poly-β-carbonyl-substrates controlled by polyketide synthases intricately governs the biosynthesis of a wide range of aromatic polyketides. Analogous small-molecule catalysed processes would conceivably induce selective cyclisations of noncanonical polycarbonyl substrates to provide products distinct from natural polyketides. Herein, we report a secondary amine-catalysed twofold cyclisation of noncanonical hexacarbonyl substrates furnishing enantioenriched tetra-*ortho*-substituted binaphthalenes. The substrates were prepared by a fourfold ozonolysis of dicinnamyl biindenes and converted under catalyst-control with high atroposelectivity. Privileged catalysts and ligands were readily accessible from the binaphthalene products stemming from the noncanonical polyketide cyclisations.

Poly-β-carbonyl chains, assembled by nonreducing polyketide synthases from acetate units, are biosynthetically diverged into a myriad of aromatic natural products. In particular their selective folding, aldol cyclisation and ensuing dehydration result in a broad range of skeletal variation, while tailoring steps further extend the diversity of the polyketide architecture (Fig. 1a).[1–3] Moreover, subsequent enzymatic dimerisations provide structurally markedly unique atropisomeric scaffolds, typically with control over the configuration of stereogenic axes.[4–6] Whereas the radical intermediates of dimerisation processes set the basis of biomimetic strategies, they also dictate the regioselectivity for *ortho*- and *para*-phenol couplings.[7,8] Taking into account that natural polyketides are restricted to a β-oxygenation pattern,[9–11] we anticipated that noncanonical[12] polyketide cyclisations governed by small-molecule catalysts would furnish valuable tetra-*ortho*-substituted atropisomeric biaryls distinct from dimerisation products. Considering the findings of stoichiometric biomimetic polyketide cyclisations,[13–18] we hence conceived a stereoselective polyketide cyclisation by means of catalytic substrate activation. More specifically, the controlled polyketide folding of substrate **2**, characterised by a noncanonical oxygenation pattern (≠β) obtained by an oxidative olefin cleavage of biindene **1**, would directly give rise to atropisomeric binaphthalenes **4** by virtue of a twofold arene-forming aldol condensation (Fig. 1b, **2**→**4**).[19–21]

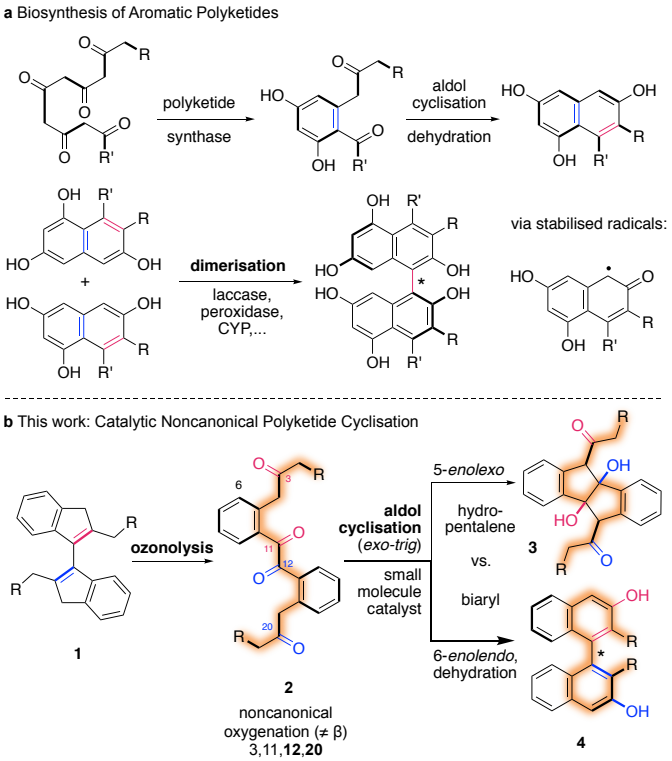

Fig. 1 | Biosynthesis of aromatic polyketides and catalytic noncanonical polyketide cyclisation. a Aldol cyclisation of poly-β-carbonyl-substrates controlled by polyketide synthases followed by an atroposelective oxidative dimerisation via stabilised radicals. **b** Ozonolysis and noncanonical polyketide cyclisation by means of double 5-*enolexo*- and twofold 6-*enolendo*-aldolisations providing hydropentalenes **3** or tetra-*ortho*-substituted biaryls **4** by a twofold atroposelective arene-forming aldol condensation.

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Notably, the respective tetra-*ortho*-carbon substituted biaryls **4** represent an ideal scaffold for catalyst design,[22] only scarcely obtained by stereoselective central-to-axial chirality conversion,[23] C-H activation,[24] [2+2+2]-cycloaddition,[25] or cross-coupling[26] strategies. The prospects of catalyst-controlled biomimetic polyketide cyclisation and the direct entry into privileged biaryl scaffolds[27] thus encouraged us to evaluate the aldolisation modes of tetraketone **2**. While considering the different folding modes of **2**, the striking versatility of polyketide cyclisations became evident by the double 5-(*enolexo*)-*exo-trig* aldolisation leading to hydropentalene product **3**, and the divergent twofold 6-(*enol-endo*)-*exo-trig* cyclisation, which efficiently provides atropisomeric binaphthyl **4** after succeeding dehydrations.[28,29] A selective aldolisation with a small-molecule catalyst that governs the configuration of the stereogenic axis would therefore enable a remarkably effective synthesis of enantioenriched biaryls **4**; another incentive for the biomimetic catalytic polyketide cyclisation.

Results

Substrate evaluation, synthesis and characterisation. We initiated our study with aryl- and alkyl-terminated substrates **2** (R = Ph, Me)[30] and interestingly, all of the tested aldolisation conditions exclusively furnished hydropentalene products **3** by 5-(*enol-exo*)-*exo-trig* cyclizations.[30,31] In contrast, initial observations suggested that particularly valuable tetra-*ortho*-substituted biaryls were formed by 6-(*enolendo*)-*exo-trig* cyclisations, when formyl-terminated substrates were employed. We consequently devised an expedient synthesis of **2a** by a notable four-fold ozonolysis (Fig. 2). Dicinnamyl biindene **1a** was suitably prepared by an oxidative dimerisation of the corresponding indene **5a** with ensuing olefin isomerisation.[32,33] The subsequent treatment with ozone and PPh_3 efficiently provided the noncanonical hexacarbonyl substrate **2a** by the cleavage of the four olefinic bonds.[34,35] Unexpectedly, the substrate **2a** was found to be stable for over 24 h in chloroform

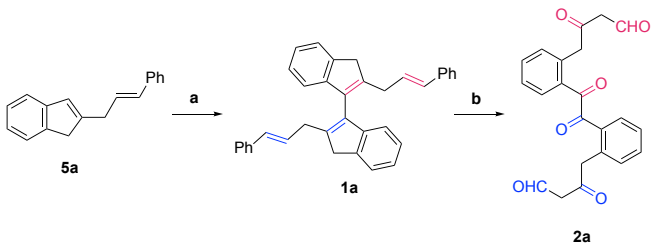
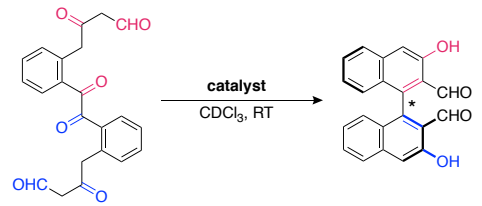


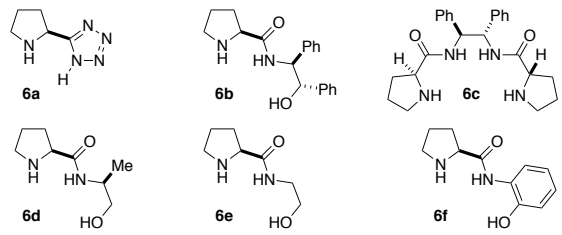
Fig. 2 | Preparation of substrates Conditions: **a** *n*-BuLi, Et_2O, –78 °C, $CuCl_2$, –78 °C to RT, *then* pyrrolidine, CH_2Cl_2, RT. 56% yield over two steps. **b** O_3, $CDCl_3$, –50 °C, *then* PPh_3, –50 °C to RT. 49% yield for 4 DBs.

at room temperature, existing as a tautomeric mixture poised for catalyst activation, as observed by NMR.[30]

Method development. With the hexacarbonyl substrate **2a** in hand, we explored the twofold 6-*enolendo* cyclisation[36] governed by small-molecule catalysts, selectively affording the atropisomeric biaryl **4a** upon formation of two new aromatic rings.[30] Gratifyingly, the desired tetra-*ortho*-substituted biaryl **4a** was obtained without detectable amounts of hydropentalenes by the use of L-proline or it's tetrazole-derivative **6a**, however in moderate yield and level of enantiocontrol (Table 1, entry 1 and 2). Systematic examination of amine and ion-pairing catalysts[30,37,38] conclusively revealed that catalyst **6b**[39] with a

Table 1 | Optimisation of the catalyst-controlled, double 6-*(enolendo)-exo-trig* cyclisation.





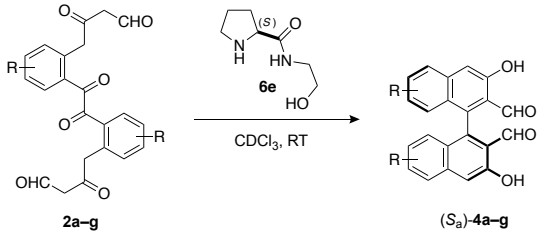
Entry	Catalyst	Time	Yield	e.r.
1	**L-Pro**	66	50	85:15
2	**6a**	48	65	67:33
3	**6b**	63	62	95:5
4	**6c**	63	74	95:5
5	**6d**	63	74	94:6
6	**6e**	48	65	96:4
7[a]	**6f**	48	67	96:4
8[a]	**6e**[b]	**66**	**82**[c]	**95:5**
9[a]	**6f**[b]	157	70[c]	94:6
10[a]	**6e**[b,d]	24	76[c]	92:8
11[a]	**6e**[e]	44	63[c]	87:13

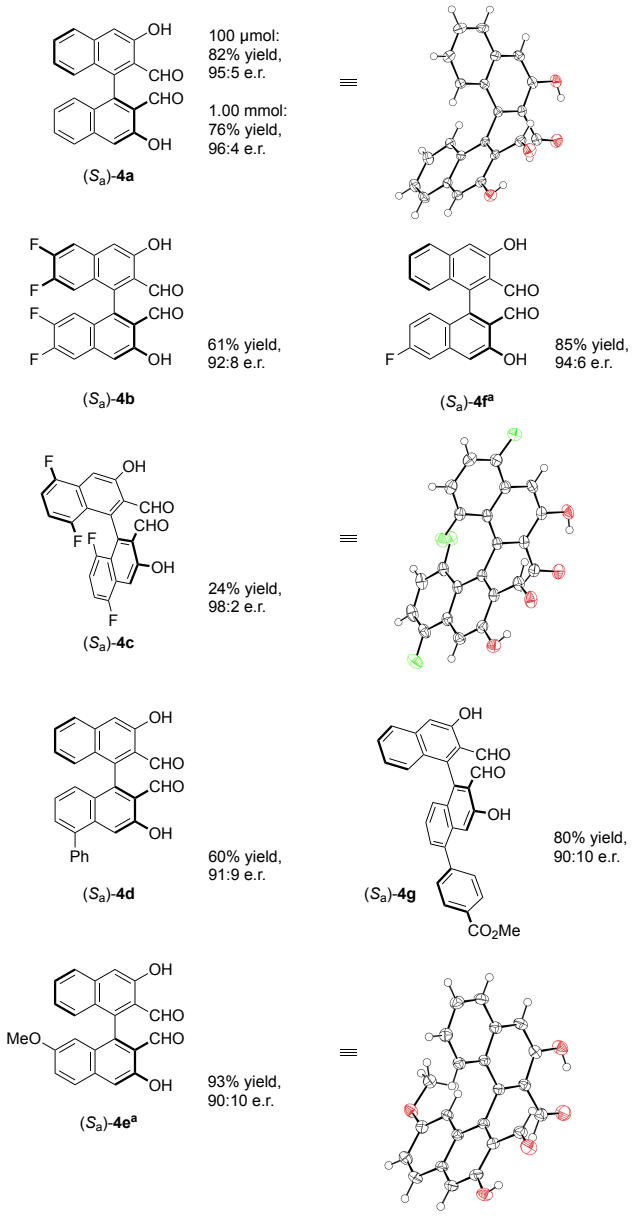
Reactions performed with 10.0 μmol substrate **2a**, in $CDCl_3$ (2.00 mmolL^{-1}) at RT with 8.00 μmol catalyst. The e.r. are determined by HPLC on a chiral stationary phase. **a** 100 μmol reaction scale. **b** 80.0 μmol of catalyst. **c** Isolated yields. **d** With 80.0 μmol trifluoroacetic acid. **e** 40.0 μmol of catalyst and 40.0 μmol of trifluoroacetic acid.

hydrogen bond donating side chain results in a significant increase in enantioselectivity (entry 3; 62% yield, 95:5 e.r.). We thus evaluated catalysts spanning a slightly larger hydrogen bond network for more stringent control of the nonenzymatic double cyclisation cascade. The bisprolineamide **6c**[40] allowed an increase in yield with similarly high atroposelectivity (entry 4; 74% yield, 95:5 e.r.) and catalyst **6d** indicated that the outcome of the reaction is marginally affected by the aminoethanol substituent (entry 5; Me in **6d**, vs. Ph groups in **6b**, 94:6 e.r.). The readily available parent aminoethanol catalyst **6e**[41] and the aminophenol-based congener **6f**[42] were consequently tested for their capacity to control the noncanonical polyketide cyclisation. Remarkably, an excellent selectivity and high yields were achieved with both catalysts, which effectively provided product **4a** on a 100 µmol reaction scale (entries 8 and 9; 82% yield, 95:5 e.r. vs. 70% yield, 94:6 e.r.). With trifluoroacetic acid (TFA) to accelerate dehydration, the reaction time could be reduced to 24 h (entry 10; 76% yield, 92:8 e.r.), while lowering the loading of the studied catalysts[30] by half affected the rate of elimination, yield and atroposelectivity (with **6e**: 63%, 87:13 e.r., 20 mol% per cyclisation). Notably, the aminoethanol catalyst **6e** is effortlessly prepared in large quantities and was therefore selected for our optimised reaction protocol.

Scope of the late-stage catalytic, noncanonical polyketide cyclisation. To establish the utility of the noncanonical polyketide cyclisation, the reaction scale was increased to 1.00 mmol, confirming that tetra-*ortho*-substituted biaryls are accessible in high yield and with excellent atroposelectivity (Table 2, 76% yield, 96:4 e.r.). We next investigated the scope and limitations of the method and evaluated the preparation of fluorinated binaphthalenes, owing to their particular value for catalyst design.[43] With a more electron deficient hexacarbonyl substrate, tetrafluoro-binaphthyl dialdehyde **4b** was obtained with an atroposelectivity of 92:8, which underlines the versatility of the developed cyclisation method. To probe the boundaries of steric interactions, we examined an extraordinarily encumbered substrate **2c**. The formation of **4c** with 98:2 atroposelectivity represents a unique synthesis of notorious tetra-*ortho*-di-*peri*- atropisomers, while the compromised yield indicates the limits for non-bonding interactions. To further demonstrate the complementarity to dimerisation approaches, we subsequently explored the cyclisation of unsymmetrically substituted substrates **2d–f** from 1,1'-biindenes synthesised by an efficient Suzuki cross-coupling of indenyl trifluoroborate and cinnamyl indanone-derived enol triflates.[30] An aryl group was readily introduced at the 5-position, providing access to the terphenyl system **4d** with an e.r. of 91:9.

Table 2 | Scope of the noncanonical polyketide cyclisation.





Reactions were performed with 50.0 µmol substrate **2b–g** in $CDCl_3$ (2.00 mmolL^{-1}) at RT with 40.0 µmol catalyst **6e**. Isolated yields. The e.r. are determined by HPLC on a chiral stationary phase. Thermal ellipsoids of the crystal structures are drawn at the 50% probability level.[44] **a** With 40.0 µmol TFA.

We next examined the effect of an electron donating group with the methoxy-substituted substrate **2e** and observed that the addition of TFA effectively accelerates the dehydration step of the cascade reaction, resulting in an excellent yield of 93% (**4e**). The inverse electronic bias of a 6-fluoro-substituent in **2f** only moderately affected the reactivity of the hexacarbonyl substrate, efficiently affording **4f** with an e.r. of 94:6 in 85% yield. Gratifyingly, the compatibility with a versatile functional group could be established by a selectively double-cyclization of an ester substrate providing (*Sa*)-**4g**, while basic amines represent a limitation of the four-fold double-bond cleavage to hexacarbonyl substrates (see SI for details).[30] The absolute configuration of the products was subsequently determined by X-ray crystallographic analysis of **4a**, **4c** and **4e**, consistently establishing that catalyst (*S*)-**6e** provides (*Sa*)-configured products.[44] The biaryl torsion angles are found between 92°–100° and the aldehyde groups are situated *syn*-periplanar to form a close hydrogen bond with the 3-hydroxy substituent. The characteristically high rotational barriers of tetra-*ortho*-substituted biaryls were consequently confirmed by atropisomerisation studies of (*Sa*)-**4a**, which revealed an exceptional configurational stability of $\Delta G^{\ddagger}_{433\,K} > 150$ kJmol^{-1} even at elevated temperature (160 °C).[30] As the significant steric interactions of configurationally stable tetra-*ortho*-substituted biaryls inherently hamper their stereoselective synthesis, we explored the mechanistic features of the noncanonical polyketide cyclisation. Interestingly, in situ NMR reaction control indicates a putative sequential twofold aldol addition followed by a double dehydration, presumably avoiding severe nonbonding interaction during the formation of the carbon-carbon bonds and thus enabling the catalyst-controlled polyketide cyclisation of encumbered substrates.[30]

Expedient syntheses of an atropisomeric ligand, catalyst and [5]helicene. To validate the utility of the method and the obtained atropisomeric linchpin products, their suitability to synthesise valuable catalysts, ligands and [5]helicene was explored with tetra-*ortho*-substituted 3,3'-dihydroxy binaphthalene (*Sa*)-**4a**. Triflation of recrystallised (*Sa*)-**4a** (e.r. > 99:1) followed by Suzuki cross-coupling yielded binaphthalene dicarbaldehyde (*Sa*)-**7** in 84% over two steps. The dicarbaldehyde (*Sa*)-**7** was efficiently converted into the chiral diene ligand (*Sa*)-**8** suitable for borane and rhodium(I) catalysis.[41,42] Furthermore, (*Sa*)-**7** was transformed into the versatile Maruoka ion-pairing catalyst (*Sa*)-**9**[47,48] through $NaBH_4$-reduction, bromination and substitution with *n*-Bu_2NH to give the quaternary ammonium salt in 82% yield over three steps. Conclusively, a viable alternative to the typically cumbersome C-H functionalisation strategies for privileged 3,3'-disubstituted atropisomers was identified. Moreover, a stereoselective route to a [5]helicene with remarkable configurational stability ($\Delta G^{\ddagger}_{333\,K}$ = 109 kJmol^{-1})[49] was elaborated by the cyclization of dibromide with LiHMDS, providing (*P*)-**10** with an e.r. of 98:2.[50] The short routes to chiral diene ligand (*Sa*)-**8**, the ion-pairing catalyst (*Sa*)-**9** and [5]helicene thus underline the virtues of retrosynthetic polyketide disconnections of aromatic systems.

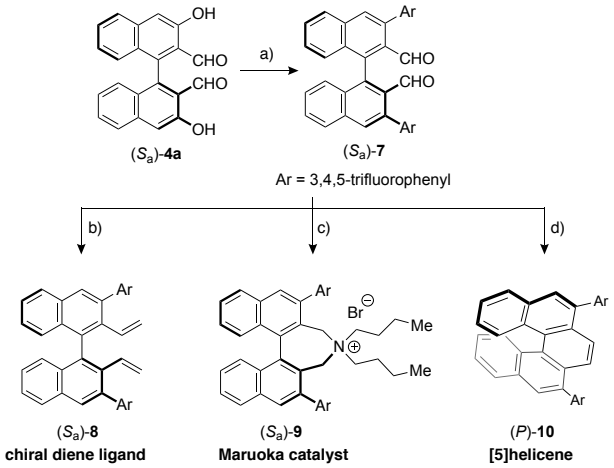


Fig. 3 | Synthesis of a chiral diene ligand, the Maruoka ion-pairing catalyst and a [5]helicene. Conditions: **a** with recrystallised (*Sa*)-**4a** (e.r. > 99:1). 1) Tf_2O, Et_3N, CH_2Cl_2, –78 °C to RT. 2) $ArB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, THF, H_2O, RT. 84% yield over two steps. e.r. > 99:1. **b** Ph_3PCH_2I, *t*-BuOK, THF, 0 °C to RT. 71% yield, e.r. > 99:1. **c** 1) $NaBH_4$, MeOH, 0 °C, *then* PBr_3, THF, 0 °C. 2) *n*-Bu_2NH, MeCN, 80 °C. 82% yield over three steps, e.r. > 99:1. **d** 1) $NaBH_4$, MeOH, 0 °C, *then* PBr_3, THF, 0 °C. 2) LiHMDS, HMPA, 0 °C. 66% yield over three steps, e.r. = 98:2; $\Delta G^{\ddagger}_{333\,K}$ =109 kJmol^{-1}.

Conclusion

In summary, we developed a small-molecule catalysed noncanonical polyketide cyclisation, affording atropisomeric tetra-*ortho*-substituted binaphthalenes distinct from natural dimerisation products. The hexacarbonyl substrates, prepared by an effective fourfold ozonolysis, were activated with an abundant secondary amine catalyst, enabling a highly atroposelective cascade reaction with up to 93% yield. The biomimetic late-stage cyclisation of noncanonical polyketides provides access to a chiral diene ligand and the Maruoka ion-pairing catalyst. Recognising the polyketide structure in the retrosynthesis of polyaromatic compounds thus allows an effective synthetic strategy and furthermore

underscores the virtues of selective nonenzymatic polyketide cyclisations. Ongoing investigations focus on the catalyst-controlled cyclisation of canonical and noncanonical polyketide substrates of different oxidation states and the rational design of small-molecule catalysts for polyketide cyclisations.

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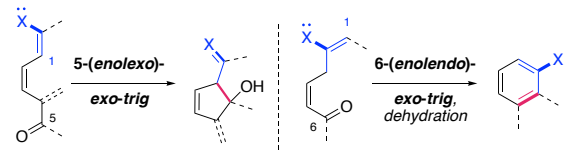
29. 

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Author contributions

R.M.W. developed the substrate synthesis and identified the aldolisation modes. R.M.W. and V.C.F. optimised the synthetic method. R.M.W. investigated the scope and synthesised the ligand and catalyst. D.H. investigated the substrate tautomerism and mechanistic features by NMR. C.S. conceived and supervised the project. All authors contributed to the preparation of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary data is available for this paper.

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