How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202212627
International Edition: doi.org/10.1002/anie.202212627
German Edition: doi.org/10.1002/ange.202212627

Atropisomers

o-Quinodimethane Atropisomers: Enantioselective Synthesis and Stereospecific Transformation

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Dedicated to Professor Wolf-D. Woggon on the occasion of his 80th birthday

Abstract: *o*-Quinodimethanes have remarkable utility as reactive intermediates in Diels–Alder reactions, enabling significantly accelerated routes to complex polycyclic compounds. The discovery of different discrete precursors to thermally generate *o*-quinodimethanes thereby greatly augmented their availability and versatility. However, due to the required high temperatures and the immense reactivity of *o*-quinodimethanes, stereoselectivity to afford isomerically defined products still constitutes a critical challenge. Herein, we describe the accessibility of atropisomeric *o*-quinodimethanes, the enantioselective synthesis of their precursors, their remarkable configurational stability and the stereospecific transformation by the benzannulation of dienophiles. A catalyst-stereocontrolled [2+2+2] cycloaddition, the generation of *o*-quinodimethane atropisomers and ensuing stereospecific Diels–Alder reactions enabled enantioselectivities through these transient intermediates with of up to 96:4 e.r.

Introduction

Owing to their exemplary ability to undergo Diels–Alder reactions, *o*-quinodimethanes (*o*-QDMs)[1] emerged as valuable intermediates for the synthesis of complex polycyclic compounds with exquisite applicability in material science,[2] fullerene chemistry[3] and the synthesis of natural products.[4] Sophisticated methods for the generation of reactive *o*-QDM intermediates were systematically established by means of 1,4-eliminations of disubstituted *o*-xylenes, cycloreversions or extrusion reactions of benzannulated heterocycles.[1,5] The majority of these methods utilize benzocyclobutene,[6] benzocyclic sulfone[7] and benzosultine[8] precursors to generate the dearomatized *o*-QDMs for efficient benzannulations to rapidly enhance the molecular complexity of dienophile substrates (Figure 1A). However, the high temperatures required for generating *o*-QDMs renders stereoselective reactions challenging and the transformation of enantioenriched *o*-QDMs has therefore yet to reach its full potential, in particular for products with different stereogenic units. Due to their well-defined topology, we hence considered atropisomeric systems as an ideal platform to induce stereoselectivity if the stereogenic axes is rendered sufficiently configurationally stable for the harsh conditions required to generate *o*-QDMs. Notably, benzannulated atropisomeric products are of pronounced significance as functional molecular systems, catalysts and as natural or unnatural bioactive compounds, which prompted the development of multiple distinct organocatalytic- and transition metal-catalyzed approaches for their stereocontrolled synthesis.[9] Cross-coupling reactions,[10] transformations of stereodynamic biaryl systems,[11] the functionalization of biaryl scaffolds[12] and stereoselective arene formation[13] thereby emerged as comprehensive strategies. Among these methods, the transition-metal-catalyzed arene-forming [2+2+2] cycloaddition was found to be particularly versatile for the synthesis of unusually congested products[13e–m] and especially chiral rhodium(I) catalysts enabled an excellent efficiency and selectivity for the enantioselective synthesis of atropisomeric biaryls from functionalized triynes.[14] Prior to these enantioselective [2+2+2] cycloadditions, Funk and Vollhardt disclosed a seminal total synthesis of (±)-estrone by combining a [2+2+2] cycloaddition with a subsequent Diels–Alder reaction through a corresponding *o*-QDM (Figure 1B).[4a] Captivated by this groundbreaking strategy, we thus questioned if a catalyst-controlled [2+2+2] cycloaddition and a subsequent thermal treatment would generate atropisomeric *o*-QDMs, representing reactive equivalents of prototypical biaryl atropisomers for stereospecific benzannulations (Figure 1C). Notably, the *ortho*-aryl substituents of atropisomeric *o*-QDMs would not only impart high bond rotational barriers, but also orient the dienophiles to influence the configuration of the newly forged stereocenters aside the encoding stereogenic axis. While Rodriguez, Coquerel and co-workers recently demonstrated the outstanding versatility

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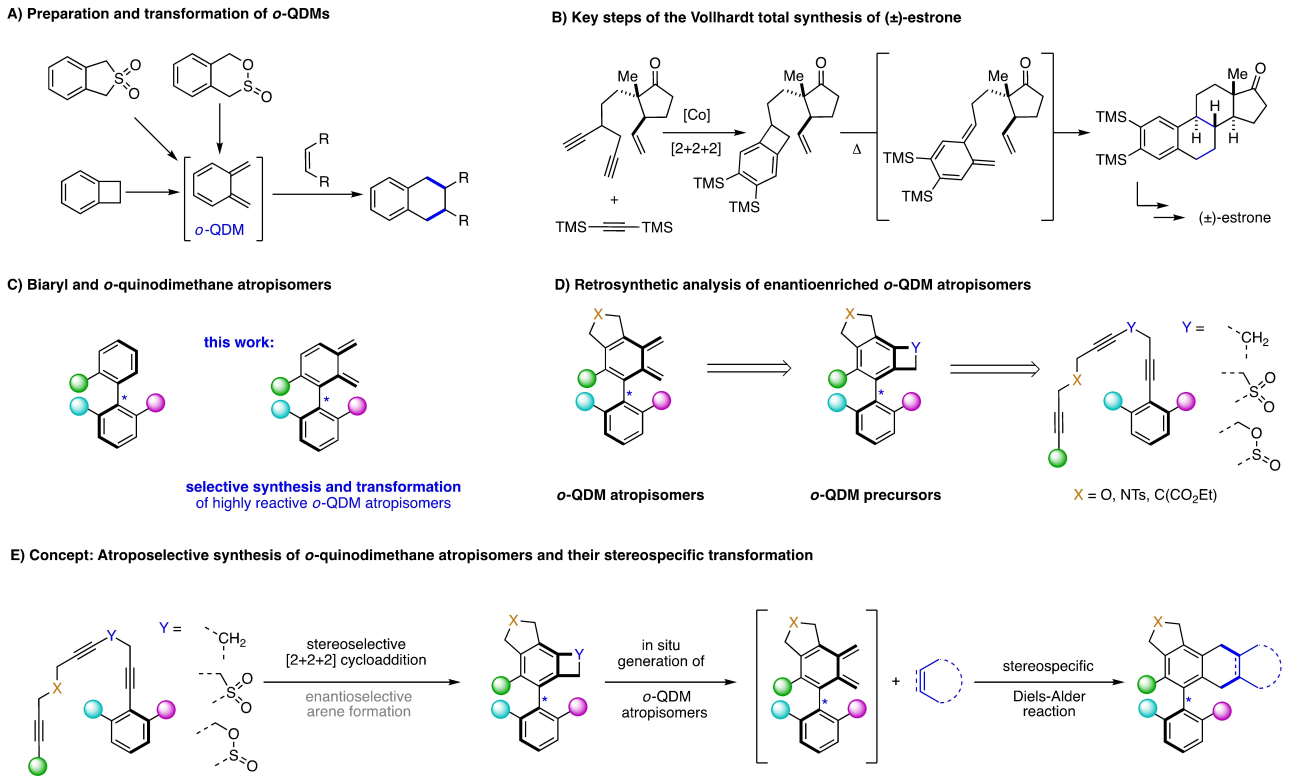


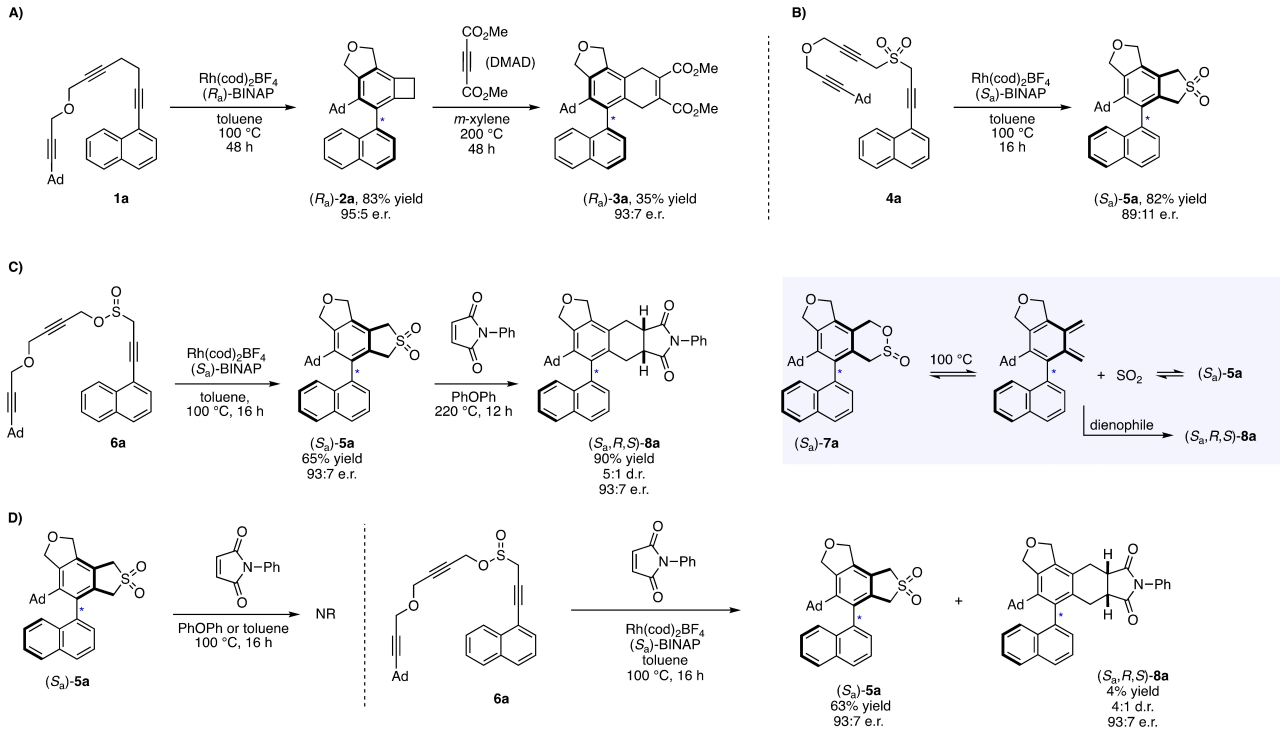
Figure 1. Background and concept of the work.

of aryne atropisomers,[15] atropisomeric *o*-QDMs would hence constitute a novel class of configurationally stable reactive atropisomers.

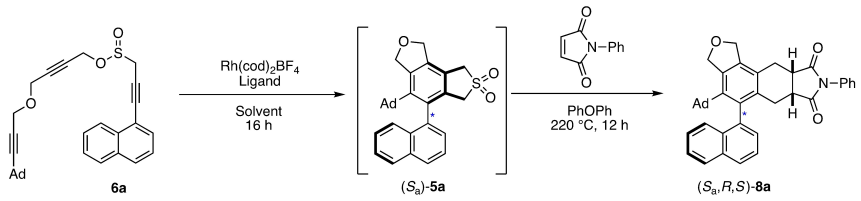
Based on our findings on the catalytic stereoselective construction of atropisomers[16] and in particular the rhodium-catalyzed [2+2+2] cycloaddition to congested triptycene products,[16c] we thus evaluated substrates allowing the catalyst-controlled enantioselective [2+2+2] cycloaddition to precursors of *o*-QDM atropisomers and the subsequent transformation in stereospecific Diels–Alder reactions. The tractability of this strategy was further unveiled in the retrosynthetic analysis, in which the unique accessibility of the triyne substrates enables a collective approach for the stereoselective intramolecular [2+2+2] cycloadditions to atropisomeric benzocyclobutene, sulfone or sultine *o*-QDM precursors by arene formation (Figure 1D). Crucially, heating these precursors generates identical *o*-QDM atropisomers for ensuing stereospecific Diels–Alder reactions with corresponding dienophiles. However, several difficulties also came to our attention, such as the congested nature of the atropisomeric *o*-QDM precursors that likely impacts the enantioselectivity of the [2+2+2] cycloaddition, the possibility for racemization of *o*-QDM atropisomers, precursors or products at the required high temperatures and the uncertain reactivity of sterically hindered *o*-QDMs in the Diels–Alder reaction. Herein, we describe that these hurdles are surmountable by the enantioselective synthesis of atropisomeric *o*-QDM precursors via the intramolecular [2+2+2] cycloaddition of triynes and the in situ generation of *o*-QDM atropisomers for subsequent Diels–Alder reactions to stereospecifically provide substituted biaryls with high efficiency and enantioselectivity over the overall reaction sequence (Figure 1E).

Results and Discussion

Our initial studies centered on the generation of *o*-QDM atropisomers from benzocyclobutene precursors and triyne **1a** was thus prepared and employed in a stereoselective Rh-catalyzed [2+2+2] cycloaddition (Figure 2A, see Supporting Information for details). To our delight, (R_a)-BINAP as ligand provided the atropisomeric benzocyclobutene (R_a)-**2a** in 83 % yield and 95:5 e.r. and the thermal ring opening followed by the Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD) confirmed the feasibility of the stereospecific benzannulation ((R_a)-**3a**: 93:7 e.r.). However, all our attempts to increase the yield remained unfruitful and partial racemization of (R_a)-**2a** was observed when the Diels–Alder reaction was conducted above 180 °C. With atropisomeric benzocyclobutenes, a racemization is hence already initiated during thermal ring opening to form the *o*-QDM. A lower temperature or a further increase of the bond rotational barrier were hence deemed necessary. Our attention was therefore turned to atropisomeric sulfone and sultine *o*-QDM precursors that undergo chelotropic ring opening or cycloreversions with SO_2 cleavage. In addition, compared to the benzocyclobutene atropisomers with the four-membered ring structure, these penta- and hexacyclic precursors for *o*-QDM atropisomers were expected to have



E) Optimization of the combined enantioselective [2+2+2] cycloaddition and stereospecific Diels-Alder reaction[a]



Entry	Ligand	Solvent	Temperature	Yield (%)[b]	d.r.[c]	e.r.[d]
1	**L1**	toluene	100 °C	47	5:1	91:9
2	**L2**	toluene	100 °C	42	4.5:1	68:32
3	**L3**	toluene	100 °C	39	5:1	84:16
4	**L4**	toluene	100 °C	69	5:1	**93:7**
5	**L5**	toluene	100 °C	64	4:1	91:9
6	**L6**	toluene	100 °C	35	4:1	80:20
7	**L4**	toluene	70 °C	55	5:1	93:7
8	**L4**	CH_2Cl_2	r.t.	40	4.5:1	83:17
9	**L4**	$ClCH_2CH_2Cl$	70 °C	31	5:1	85:15
10[e]	**L4**	PhOPh	100 °C	66	3.5:1	91:9
11[f]	**L4**	toluene	100 °C	46	5:1	93:7

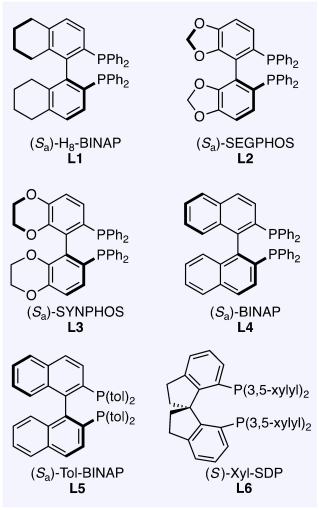


Figure 2. Initial results for the stepwise synthesis by the atroposelective [2+2+2] cycloaddition followed by the transformation of *o*-QDM precursors for stereospecific Diels–Alder reactions and the optimization of the combined sequence. A) *o*-QDMs from a benzocyclobutene substrate **1a**; B) from sulfone substrate **4a**; C) from sulfinic acid ester substrate **6a**; D) Control reactions for the transformation of (S_a)-**7a** to (S_a)-**5a**; E) Optimization: [a] $Rh(cod)_2BF_4$ (20.0 mol%) and the ligand (20.0 mol%) were dissolved in CH_2Cl_2 (5 mL) and the resulting mixture was stirred for 20 minutes. A hydrogen atmosphere (1 atm) was introduced, the mixture was stirred for 1 h to activate the Rh catalyst and the solvent was removed. The reactions were performed with **6a** (50 μmol) and this activated Rh catalyst in the specified solvent (10 mL) and temperature for 16 h. Upon filtration (SiO_2), the Diels–Alder reaction was performed with *N*-phenylmaleimide (3.00 equiv) in diphenyl ether (500 μL) at 220 °C for 12 h. [b] Isolated yield for the combined sequence. [c] Determined by ^1H NMR and confirmed by HPLC. [d] Determined by HPLC on a chiral stationary phase after isolation. [e] No solvent and catalyst removal after the [2+2+2] cycloaddition. [f] 10.0 mol% $Rh(cod)_2BF_4$ and 10.0 mol% ligand. Ad: adamantyl. NR: no reaction.

significantly increased bond rotational barriers to endure the necessary temperatures for *o*-QDM formation in the direct stereospecific Diels–Alder reactions. We thus prepared the trialkynyl sulfone substrate **4a** and the analogous sulfinic

acid ester **6a** (see Supporting Information for details).[8d,17] Gratifyingly, the [2+2+2] cycloaddition of the sulfone **4a** to atropisomeric (S_a)-**5a** resulted in 82 % yield and 89:11 e.r. with the catalytic system used for the benzocyclobutene (R_a)-**2a** (Figure 2B). Interestingly, when the sulfinic acid ester **6a**[17] was employed as substrate for the [2+2+2] cycloaddition, the identical cyclized sulfone (S_a)-**5a** was received in leu of the sultine (S_a)-**7a** through a thermal rearrangement (Figure 2C).[8d] In this case, the Rh/(S_a)-BINAP catalyst provided the atropisomeric sulfone (S_a)-**5a** with an enhanced selectivity of 93:7 e.r. Since we previously encountered purification issues with (R_a)-**3a** obtained with DMAD presumably due to partial aromatization of the dihydronaphthalene moiety, we next conducted the stereospecific Diels–Alder reaction of the atropisomeric sulfone (S_a)-**5a** with *N*-phenylmaleimide to further optimize the Diels–Alder reaction. Notably, no conversion took place when the temperature was below 200 °C (see Supporting Information for details) and we were pleased to find satisfactory results both in terms of yield and enantioselectivity for (S_a,*R*,*S*)-**8a** when we heated the reaction in PhOPh to 220 °C (90 % yield, 5:1 d.r., 93:7 e.r.). To evaluate the generation of the *o*-quinodimethane atropisomer intermediate and the transformation of the sultine precursor (S_a)-**7a** to the cyclic sulfone (S_a)-**5a** after the [2+2+2] cycloaddition, we carried out control reactions and thereby gained valuable insights (Figure 2D). As expected, no product was detected when the Diels–Alder reaction of (S_a)-**5a** was conducted at 100 °C and remarkably, when the [2+2+2] cycloaddition and the Diels–Alder reaction were performed simultaneously at 100 °C, the cycloaddition product (S_a)-**5a** was isolated in 63 % yield accompanied with 4 % of the Diels–Alder product from *N*-phenylmaleimide (S_a,*R*,*S*)-**8a** (see Supporting Information for details). These experiments indicate that the sultine product (S_a)-**7a** extrudes SO_2 at 100 °C[8b,c] to give the reactive *o*-QDM intermediate which is then trapped again by SO_2 or the dienophile, resulting in the cyclic sulfone product (S_a)-**5a** and the Diels–Alder product (S_a,*R*,*S*)-**8a**. It is also pertinent to note that heating products (R_a)-**3a** or (S_a,*R*,*S*)-**8a** to 230 °C for 6 hours did not diminish their enantioenrichment (<1 % racemization), confirming the exceptional configurational stability in both cases (see Supporting Information for details). To elaborate the simultaneous transformation at 100 °C (see Supporting Information, Table S6 for details), we performed the reaction under reduced pressure to remove SO_2 (400 mbar) and obtained (S_a,*R*,*S*)-**8a** in 28 % yield. However, lower pressures using other solvents or the addition of SO_2 capture reagents again resulted in (S_a)-**5a** as the major product, indicating the high reactivity of the *o*-quinodimethane intermediate with SO_2. Since the studies on the separate [2+2+2] cycloadditions of **6a** and Diels–Alder reactions through (S_a)-**5a** established a high stereoselectivity, stability and conversion, we combined this reaction sequence to further streamline the method (Figure 2E). Consistent with our initial results, the Rh/(S_a)-BINAP catalyst provides the product of the sequence in good yield and enantioselectivity (entry 4, 69 % yield over both stages, 5:1 d.r., 93:7 e.r.). The evaluation of chiral bisphosphine ligands revealed that other BINAP-type ligands provide slightly lower yields and enantiomeric enrichment after the benzannulation of the dienophile (entries 1–5). The spirocyclic diphosphine ligand (*S*)-xyl-SDP (**L6**) which was ideal for the rhodium-catalyzed [2+2+2] cycloaddition to triptycene-based atropisomers[16c] gave a low yield and moderate enantioselectivity (entry 6, 35 % yield, 4:1 d.r., 80:20 e.r.). Furthermore, decreasing the temperature to 70 °C resulted in the same enantioselectivity of 93:7, but the yield was reduced to 55 % (entry 7). Changing the solvent to CH_2Cl_2 or 1,2-dichloroethane also lowered the yield and e.r. (entries 8 and 9), while using the same solvent (PhOPh) as in the Diels–Alder reaction led to good yield and atropisomeric enrichment (entry 10, 66 % yield, 3.5:1 d.r., 91:9 e.r.). Finally, decreasing the amount of catalyst and ligand to 10 mol % gave the same enantioselectivity of 93:7 with a compromised yield (entry 11, 46 %). The most favorable outcome of the sequence was therefore identified with **L4** in toluene (entry 4), which we used for the remainder of the study. With the optimal reaction conditions in hand, we set out to verify the generality of the synthesis and consequent transformation of *o*-QDM atropisomers by exploring the substrate scope (Figure 3). The reaction scale was successfully increased to 100 μmol without affecting selectivity, providing (S_a,*R*,*S*)-**8a** in 70 % yield with an e.r. of 92:8. The X-ray crystallographic analysis of **5a** and **8a** established an (S_a)-configuration of the stereogenic axis, while the stereocenters are configured as expected by the shielding of the atropisomeric *o*-QDM.[18] We next evaluated the stereospecific Diels–Alder reactions with a set of representative dienophiles. More specifically, *N*-aryl maleimides with different substituents on the *N*-aryl group, such as bromide or ketone as suitable reactive handles were found to be compatible, giving (S_a,*R*,*S*)-**8b** and (S_a,*R*,*S*)-**8c** with good enantio- and diastereoselectivity (4.5:1 and 5.5:1 d.r.). *N*-(Carbomethoxy)maleimide as dienophile gave a lower yield for (S_a,*R*,*S*)-**8d** but an increased selectivity of 93:7 e.r. with a d.r. of 5:1. In these four cases (S_a,*R*,*S*)-**8a–d**, the diastereomers were obtained with good stereocontrol, indicating a dienophile preorganization by the *o*-QDM atropisomer that induces diastereoselectivity. Notably, trapping *o*-QDM atropisomeric precursor (S_a)-**5a** with maleic anhydride proceeded smoothly with an e.r. of 91:9, but with a lower d.r. of 3.5:1 to afford product (S_a,*R*,*S*)-**8e**. The reduced diastereoselectivity may be due to the lower steric hindrance of maleic anhydride relative to *N*-aryl maleimides. Dimethyl maleate as the dienophile afforded the corresponding product (S_a,*R*,*S*)-**8f** in 2.5:1 d.r. with 93:7 e.r. While fullerene derivatives where not obtained (see Supporting Information for details), fumaronitrile as smaller dienophile was also reactive with atropisomeric *o*-QDMs and gave the product (S_a,*R*,*R*)-**8g** in 92:8 and 91:9 e.r. with a d.r. of 2.0:1. The impact of the adamantyl group was next investigated as sterically demanding *ortho*-substituents greatly influence the bond rotational barrier of the atropisomeric precursors, intermediates and products. When the adamantyl group was replaced by a *tert*-butyl group, the product (S_a,*R*,*S*)-**8h** with *N*-phenylmaleimide as the dienophile could be observed with 91:9 e.r. and 3.5:1 d.r. The selectivity of the [2+2+2] cycloaddition

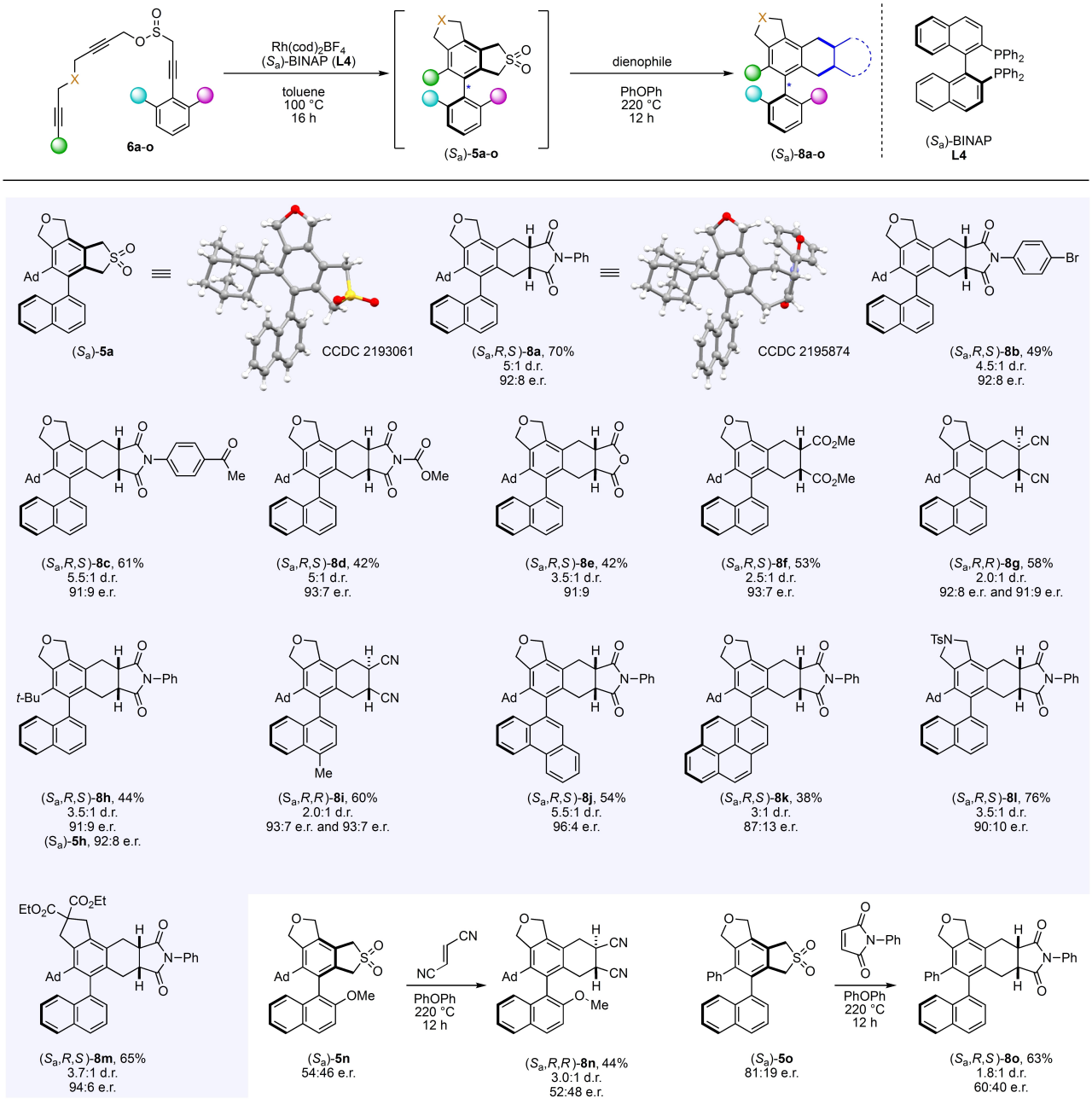


Figure 3. Scope of the synthesis and transformation of *o*-quinodimethane atropisomers. $Rh(cod)_2BF_4$ (20.0 mol%) and indicated ligand (20.0 mol%) were dissolved in CH_2Cl_2 (10 mL) and the resulting mixture was stirred for 20 minutes. A hydrogen atmosphere (1 atm) was introduced, the mixture stirred for 1 h to activate the Rh catalyst and the solvent was removed. The reactions were performed with **6a–o** (100 μmol) and this activated Rh catalyst in toluene (25 mL) at 100 °C for 16 h. Upon filtration (SiO_2), the Diels–Alder reaction was performed with the dienophiles (3.00 equiv) in diphenyl ether (1.0 mL) at 220 °C for 12 h. Isolated yields. The d.r. values were measured by ^{1}H NMR and the e.r. values of isolated products were determined by HPLC on a chiral stationary phase.

leading to the corresponding sulfone intermediate (*S*$_a$)-**5h** was also successfully established, providing an e.r. of 92:8 and confirming that almost no racemization of the sulfone intermediate (*S*$_a$)-**5h** takes place at 220 °C. We then directed our attention to the impact of the polyaromatic structure on reactivity and selectivity and were pleased to find that triyne substrates **6i–k**, possessing various polyaromatic residues such as substituted naphthyl, phenanthrene and pyrene units are suitable to provide the corresponding products **8i–k** with high enantioselectivities. Furthermore, the influence of the tether moiety was investigated by changing the oxygen-linked **6a** to a nitrogen-bridged triyne **6l** or diethyl malonate **6m**. To our delight, the triyne with the tosylamide linkages provided a good yield and selectivity ((S$_a$,*R*,*S*)-**8l**, 76% yield over both stages, 3.5:1 d.r., 90:10 e.r.) and the diethyl malonate tether was also applicable, giving the product

(S_a,*R*,*S*)-**8m** in 65 % yield for the combined sequence (94:6 e.r., 3.7:1 d.r.). While confirming the scope, we also encountered limitations that further frame the range of application. The triyne substrate (**6n**) bearing a naphthyl *ortho*-OMe group led to the tetra-*ortho* substituted precursor (S_a)-**5n** with low enantioselectivity (54:46 e.r.) and benzannulated (S_a,*R*,*S*)-**8n** was consequently obtained in 44 % yield in nearly racemic form. The increased d.r. of 3.0:1 compared to (S_a,*R*,*R*)-**8g** and **8i** is possibly attributable to the higher rigidity of the tetra-*ortho* substituted *o*-QDM atropisomer. When changing the adamantyl group to a phenyl group, the *o*-QDM atropisomer precursor (S_a)-**5o** was isolated with 81:19 e.r., but the Diels–Alder reaction at 220 °C resulted in product (S_a,*R*,*S*)-**8o** with an enantioenrichment of only 60:40 e.r. These results confirm the prerequisite for pronounced configurational stability of the topologically well-defined reactive atropisomers for the stereoselective transformations at these markedly elevated temperatures.

Conclusion

In conclusion, we describe the formation and viability of *o*-quinodimethane atropisomers for stereoselective synthesis. The three main *o*-QDM precursors were atroposelectively prepared by the rhodium-catalyzed intramolecular [2+2+2] cycloaddition of corresponding triynes. The exceptional configurational stability of the sulfinic acid ester precursors allowed a thermal in situ ring opening to *o*-QDMs atropisomers with defined configuration, which stereospecifically react in Diels–Alder reactions with dienophiles by benzannulation to form complex substituted biaryl atropisomers with high enantiomeric enrichment. With atropisomeric *o*-QDMs established as reactive intermediates with exceptional configurational stability and versatility, we anticipate that *o*-QDM atropisomers will open avenues for the expeditious preparation of stereochemically defined polycyclic aromatics.

Acknowledgements

We gratefully acknowledge the Swiss National Science Foundation (175746), the University of Basel, and the NCCR Molecular Systems Engineering (182895) for financial support. 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 Prof. D. Häussinger for NMR and Dr. A. Prescimone for X-ray crystallography. Open access funding was provided by the University of 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: Atropisomers · [2+2+2] Cycloaddition · Diels–Alder Reaction · Stereoselectivity · *o*-Quinodimethane

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Manuscript received: August 26, 2022
Accepted manuscript online: October 18, 2022
Version of record online: November 10, 2022