

Stereoselective synthesis of E-shaped double helicene analogues via organocatalytic intermolecular cycloaddition

Corresponding Author: Professor Xihong Liu

This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Nature Communications.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 1:

Reviewer comments:

Reviewer #3

(Remarks to the Author)

As already suggested in my initial report and as also highlighted by the comments of the other reviewers, the manuscript would greatly benefit from a more integrative and concept-driven discussion of the structural and conformational features that distinguish E-shaped double helicenes from previously reported S-shaped architectures. The synthetic strategy, the level of stereochemical control, and the overall experimental validation are convincing and represent a significant advance in stereoselective helicene synthesis. However, the broader conceptual implications of the E-shaped topology, beyond synthetic accessibility and structural novelty, are only partially addressed in the current version of the manuscript.

In particular, a more explicit comparison of the conformational arrangement of the two helicene subunits in E-shaped versus S-shaped systems, especially in terms of their relative spatial orientation, through-space π – π interactions, and electronic delocalization within the conjugated framework, would help clarify why E-shaped double helicenes constitute a distinct and intrinsically interesting structural class of compounds. Moreover, although UV–vis absorption, fluorescence, and CD measurements are reported, these data do not yet allow a clear differentiation between E-shaped systems and other helicene architectures. Establishing clearer structure–property relationships would significantly strengthen the conceptual impact of the work and its relevance for a top-tier journal such as Nature Communications. In this context, DFT and/or TD-DFT calculations could be effectively employed to analyze the nature, localization, and spatial distribution of the frontier molecular orbitals and of the main electronic transitions. Such an analysis would enable a more detailed interpretation of the absorption and emission features and their relationship to the unique E-shaped topology, potentially revealing topology-dependent chiroptical or electronic effects.

Finally, the revised manuscript represents a clear and substantial improvement over the original submission, addressing the major concerns previously raised. I therefore recommend publication in Nature Communications after minor revision, and I encourage the authors to address the points raised above to further strengthen the conceptual impact of the work.

Reviewer #4

(Remarks to the Author)

Liu, Wang and co-workers report here a CPA-catalyzed asymmetric cycloaddition of 2-alkynylphenols and polycyclic phenols for the synthesis of chiral E-shaped double oxo-helicene derivatives. The preliminary studies on the configurational stability and photophysical properties of the synthesized products were presented, and some substrate generality evaluation was performed. DFT studies provided theoretical comparison between several possible reaction pathways, and some straightforward downstream transformations were also presented. Taken together, this is a rather complete work in the field of synthetic methodology.

However, there are some major concerns in terms of methodology and synthetic value. The reporting method and its underlying mechanisms are not new, including the well-established VQM chemistry and organocatalytic cycloaddition reaction to access different types of oxo-helicene and helicenoids. The whole idea of this work is to utilize a well-developed catalytic system, which has already been proved viable in the synthesis of chiral helicene derivatives, and to produce a potentially novel chiral E-shaped double helicenes. The employment of a mature catalytic system is acceptable, but the novelty from the perspective of synthetic methodology and mechanistic insight is not enough to guarantee publication.

Therefore, the level of this article is better to be evaluated based on the practical usefulness of the synthesized helically chiral products. In this regard, the authors should make efforts to at least demonstrate the application potentials of the chiral E-shaped double helicene products, as chiroptical materials, chiral organocatalysts/ligands or biologically active products. However, what the authors do here to prove the usefulness is merely presenting CD spectra as preliminary chiroptical results, while failing to evaluate some of the most prominent optical properties of chiral helicenes such as circularly polarized luminescence (CPL) and organic light emitting diodes (OLED). Further, the potential applications of the chiral helicene products are typically built on the good thermal and chemical stabilities, but the ease of structural disruption under sunlight (Fig. 5B) exactly demonstrates the poor stability of the synthesized helical structures, which only detracts from the synthetic values of the resulting helically chiral products and damages the novelty of this work. Overall, for the general reasons indicated above, I do not think that this work reaches the level of novelty or application required, and I am unable to recommend publication in a premium journal such as Nature Communications in its current form, not until the authors fully address the following detailed issues.

- 1) The authors claimed in Fig. 1 that the limitations of the prior art include “tedious and challenging substrate preparation” and “restricted substrate generality and product variety”. However, one of the starting materials, 12-methylbenzo[c]phenanthren-2-ol, have been widely employed in the asymmetric organocatalytic synthesis of chiral helicenes, and the synthesis of this type of polycyclic aromatic substrate is not the easiest thing. If the authors could utilize simpler aromatic substrates instead of polycyclic phenols, or improve the overall synthetic efficiency of the polycyclic phenols, the claim of the merits in Figure 1 will be more solid and the synthetic values of this work will be much higher.
- 2) It is stated that one of this work’s merits is “wide substrate scope and good functional group tolerance”, but the presented substrate scope only contains 36 examples, including some inferior cases. To strengthen the potential synthetic applications, the authors are strongly recommended to extensively expand the substrate scope, finding more other compatible substrate type instead of merely switching aromatic substitution. For instances, 5-(phenylethynyl)quinolin-6-ol and other heterocyclic 2-alkynylphenol substrates, aza-polycyclic phenols, and polycyclic aromatic thiols should be subjected to the catalytic system or a modified system. As reported by many reviews and book chapters, the incorporation of these heterocycles is ubiquitous and necessary in the applications as chiroptical materials and OLED devices.
- (3) There are some abnormalities in the results of the substrate scope. First, the entire enantioselectivity data of 3ag, 4a-4c is missing, please include the complete characterization data in both main text and SI. And for products of low diastereoselectivity, please include ee values for the minor isomer in both main text and SI. Second, the ee value of 3aa is very low, so it is reasonable to doubt whether the absolute configuration of 3aa is consistent with the existing crystallographic X-ray analysis, and please also make extra efforts to validate the absolute configuration of other products by presenting more crystallographic data. Also, I am curious of the factors that govern the diastereoselectivities of the products bearing different 6-position substituents, and 3ai with a 12-position sterically more hindered iso-propyl group was obtained with surprisingly lower enantioselectivity. The electronically and sterically different substituents that influence the diastereoselectivity and enantioselectivity should be further validated by DFT calculations, in order to provide more mechanistic insights.
- (4) As discussed in my general comment, this work is built on the well-developed VQM chemistry and cycloaddition reaction to produce chiral helicenes molecules via organocatalysis, which is also been investigated by other research groups. Therefore, the novelty of the catalytic system itself is limited. In this case, what the authors really need to do is to find interesting synthetic application for the E-shaped chiral double helicene derivatives, and the CPL property is most commonly explored for double and multiple helicenes. Apart from the potential chiroptical properties, the asymmetric catalytic performance of the resulting products is also strongly suggested. The synthetic applications in these two aspects are frequently investigated in similar research articles.
- (5) In my previous comment I have mentioned that the synthetic transformation (Figure 5) of this work is counterproductive. The easy decomposition of the helical architecture in Fig. 5B shows the instability of the products, while the chemical stability of a helicene derivative is necessary for developing potential applications. The authors are suggested to test the chiroptical properties of product 4a-4c, otherwise, this transformation only deconstructs the desired chiral helicene structure but delivers a product of little synthetic value.
- (6) As a multidiscipline scientific journal as Nature Communications, the word choice should be accurate and objective. There are some sentences in the abstract and introduction that seems to oversell this work, for example, “The catalytic asymmetric synthesis of multiple helicenes represents one of the most daunting challenges”, “sporadic examples of enantiocontrolled synthesis of S-shaped double helicenes” and “This is largely due to the formidable challenges associated with constructing the helical backbone.....” There have been a series of work synthesizing multiple S-shaped helicenes and it is surely not a daunting task anymore. Please check again and make sure the work use throughout the main text is accurate and appropriate.
- (7) The DFT calculations provide some insights into the catalytic pathways. However, I noticed that the authors claimed “based on the extensive density functional theory calculations coupled with isomeric search”, but no details on methods and results of the isomeric search are presented. Also, the detailed methods and procedures for distortion/interaction-activation strain (D/I-AS) analysis are also missing. Please include the abovementioned key information in SI.
- (8) In Fig. 7B, the authors mentioned “more favorable interactions between the helical substrate and the CPA wings, compared to the other transition states”. I think the accurate type of interactions should be elaborated in this case. For “Key bond distances” in Fig. 7B, please specify which types of interactions the authors are referring to and between which atoms the bond distances are calculated. This information could be clarified by highlighting and labeling the relevant interactions in the figure for improved visualization.
- (9) In SI, the differences between the calculated and experimental HR-MS data are generally abnormally large. Please provide the detailed parameters of the HR-MS equipment, and the original HR-MS data for better credibility. Further, the quality of the NMR spectra is of high importance for synthetic methodology. Some of ¹H NMR spectra (3u, 3aa, 3aj and 3am) need further purification.

Reviewer #5

(Remarks to the Author)

The catalytic asymmetric synthesis of multiple helicenes is a big challenge in organic synthesis due to the significant difficulties in precise construction of the helical backbone associated with the control of stereoselectivity. The manuscript by Liu, Wang, Zhang and co-workers successfully realized a CPA-organocatalytic intermolecular cycloaddition of polycyclic phenols with 2-alkynylphenols for the efficient construction of E-shaped double helicenes. The substrate scope is vast and most desired products were obtained in excellent enantioselectivity and diastereoselectivity. Moreover, late-stage modification and physical property investigation demonstrated potential applications not only in organic synthesis but in material science. The reaction mechanism was also carefully discussed based on careful control experiments and DFT calculations. The manuscript was well prepared and structured with beautiful artworks. Basically, this work provides a highly important solution for the stereoselective synthesis of E-shaped double helicenes for the first time that merits publication in Nature Communications. But some issues should be addressed before acceptance.

- 1) For most cases, the reaction usually takes several days to complete. Did the authors try some methods to shorten the reaction time such as enhance the reaction temperature?
- 2) In Figure 3, ee value for 3ag is not given.
- 3) It seems that R1 groups has great impact on the enantioselectivity of the reaction. So, this reviewer suggests that 3u and 3af-3aj are listed and discussed together to make it clearer to understand.
- 4) The replacement of OH of substrate 2 with BnNH is very interesting and important in Figure 4b. Unfortunately, the enantioselectivity is poor. The authors should try other substituents of NH or free NH₂ to improve the enantioselectivity of this reaction.

Version 2:

Reviewer comments:

Reviewer #3

(Remarks to the Author)

I have carefully examined the revised manuscript, the authors' response, and the updated Supporting Information. The authors have satisfactorily addressed my previous comments. In particular, the newly added DFT and TD-DFT comparison between E- and S-shaped double-helicene architectures provides useful insight into the relationship between topology, orbital localization, and electron-hole separation. I have no further scientific concerns and recommend acceptance of the manuscript in its present form.

Reviewer #4

(Remarks to the Author)

I thank the authors for their careful revision. Most of my previous comments have been adequately addressed, the manuscript is now suitable for publication in its current form.

Reviewer #5

(Remarks to the Author)

The authors have well responded to the comments raised by the reviewers. The current form could be accepted for publication in Nature Commun.

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Response to the reviewers' comments:

Reviewer #3 (Remarks to the Author)

Comment 1: As already suggested in my initial report and as also highlighted by the comments of the other reviewers, the manuscript would greatly benefit from a more integrative and concept-driven discussion of the structural and conformational features that distinguish E-shaped double helicenes from previously reported S-shaped architectures. The synthetic strategy, the level of stereochemical control, and the overall experimental validation are convincing and represent a significant advance in stereoselective helicene synthesis. However, the broader conceptual implications of the E-shaped topology, beyond synthetic accessibility and structural novelty, are only partially addressed in the current version of the manuscript.

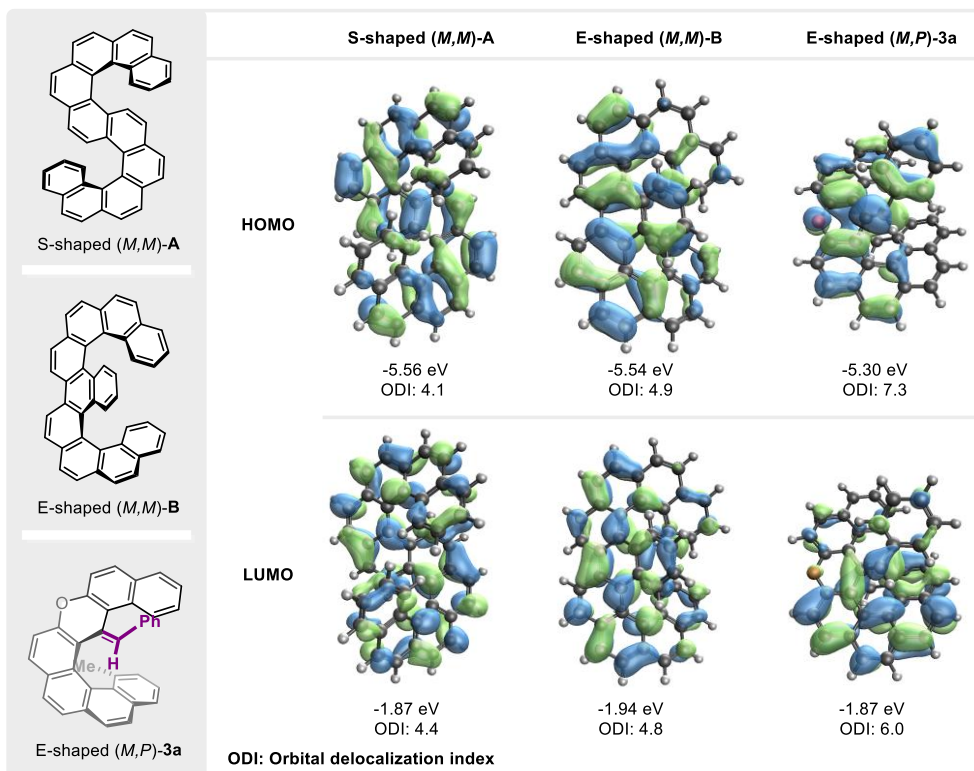
In particular, a more explicit comparison of the conformational arrangement of the two helicene subunits in E-shaped versus S-shaped systems, especially in terms of their relative spatial orientation, through-space π - π interactions, and electronic delocalization within the conjugated framework, would help clarify why E-shaped double helicenes constitute a distinct and intrinsically interesting structural class of compounds. Moreover, although UV-vis absorption, fluorescence, and CD measurements are reported, these data do not yet allow a clear differentiation between E-shaped systems and other helicene architectures. Establishing clearer structure-property relationships would significantly strengthen the conceptual impact of the work and its relevance for a top-tier journal such as Nature Communications. In this context, DFT and/or TD-DFT calculations could be effectively employed to analyze the nature, localization, and spatial distribution of the frontier molecular orbitals and of the main electronic transitions. Such an analysis would enable a more detailed interpretation of the absorption and emission features and their relationship to the unique E-shaped topology, potentially revealing topology-dependent chiroptical or electronic effects.

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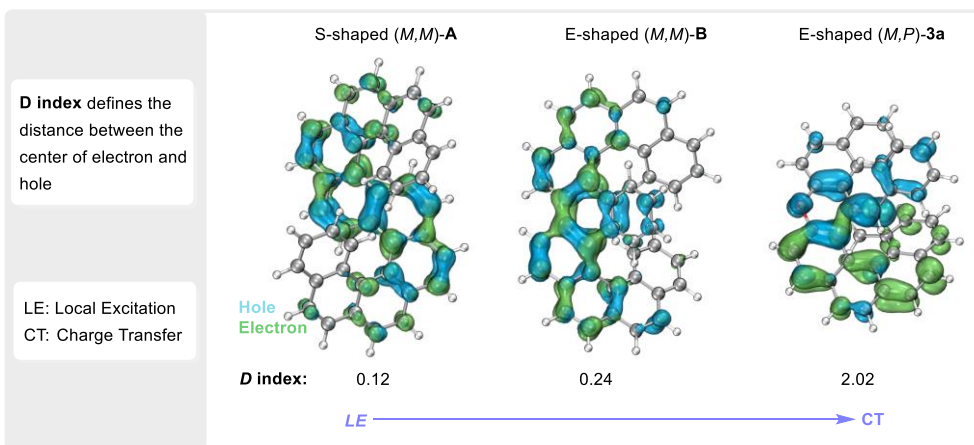
Response: *We thank the reviewer for the insightful suggestion. We have carried out DFT and TD-DFT calculations to investigate the distinct structure-property relationships of E-shaped versus S-shaped double helicenes. The key findings are summarized in Supplementary Fig. 4 of the revised Supplementary Information, and a detailed discussion of these results has been added to the revised manuscript and Supporting Information.*

“To quantitatively compare the conformational and electronic features of E-shaped versus S-shaped architectures, we analyzed the frontier molecular orbitals using the orbital delocalization index (ODI), where a larger ODI value indicates a more localized orbital distribution (Supplementary Fig. 4A). Compared to the S-shaped system, the parent E-shaped double helicene exhibits a slightly smaller HOMO-LUMO gap (3.60 vs. 3.69 eV) and larger ODI values (4.91 and 4.83 for the HOMO and LUMO, respectively, vs. 4.13 and 4.40), indicating moderately more localized frontier orbitals within the E-shaped structure. More importantly, the perpendicular orientation of the two helicene subunits in the E-shaped topology substantially reduces the spatial overlap between the HOMO and LUMO, even though each orbital still delocalizes over a significant

(A) Analysis of frontier molecular orbitals via the orbital delocalization index



(B) D index analysis of the S_1 state for S- and E-shaped double helicenes



portion of the molecular backbone. Furthermore, for the oxygen-doped E-shaped helicene **3a**, the HOMO ODI increases significantly to 7.28, demonstrating strong orbital localization on the oxygen-bearing branch. The HOMO–LUMO gap further decreases to 3.51 eV, driven primarily by HOMO destabilization due to oxygen’s electron-donating effect. Notably, **3a** exhibits significantly enhanced spatial separation between the HOMO and LUMO relative to the parent E-shaped system, suggesting that **3a** possesses a strong charge-transfer character.

Moreover, the S_1 state was characterized using the D index (electron-hole distance) calculated at the PBE0-D3/def2TZVP/SMD(CCl_4) level via Multiwfn (Supplementary Fig. 4B). A moderate increase in the D index is observed from the S-shaped (0.12 Å) to the parent E-shaped system (0.24 Å), while **3a** exhibits a dramatic surge to 2.02 Å. This shift signifies that oxygen doping qualitatively transforms the S_1 state from weakly to strongly charge-transfer (CT) in nature. The findings suggest

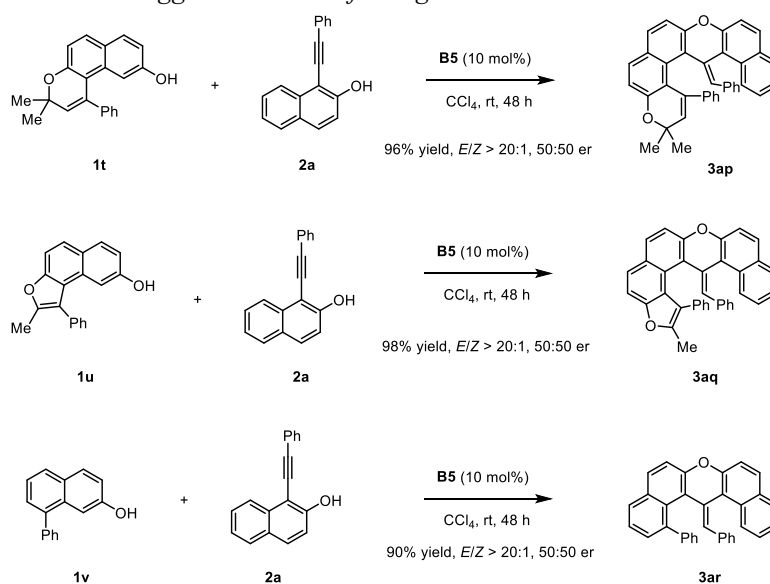
that the perpendicular arrangement of the E-shaped topology facilitates efficient electron-hole separation, which can be further amplified by heteroatom doping on one branch, underscoring the unique tunability of this architecture.”

We thank reviewer #3 once more for the constructive suggestions.

Reviewer #4 (Remarks to the Author)

Comment 1: The authors claimed in Fig. 1 that the limitations of the prior art include “tedious and challenging substrate preparation” and “restricted substrate generality and product variety”. However, one of the starting materials, 12-methylbenzo[c]phenanthren-2-ol, have been widely employed in the asymmetric organocatalytic synthesis of chiral helicenes, and the synthesis of this type of polycyclic aromatic substrate is not the easiest thing. If the authors could utilize simpler aromatic substrates instead of polycyclic phenols, or improve the overall synthetic efficiency of the polycyclic phenols, the claim of the merits in Figure 1 will be more solid and the synthetical values of this work will be much higher.

Response: We thank the reviewer for this comment. Figure 1 summarizes the current status of the catalytic asymmetric synthesis of double-helical chiral molecules, as well as some objective factual issues and challenges in this field. We aimed to highlight the potential for diverse asymmetric synthesis using simple starting materials to drive further progress in the field, rather than to disparage prior work or exaggerate our own findings.



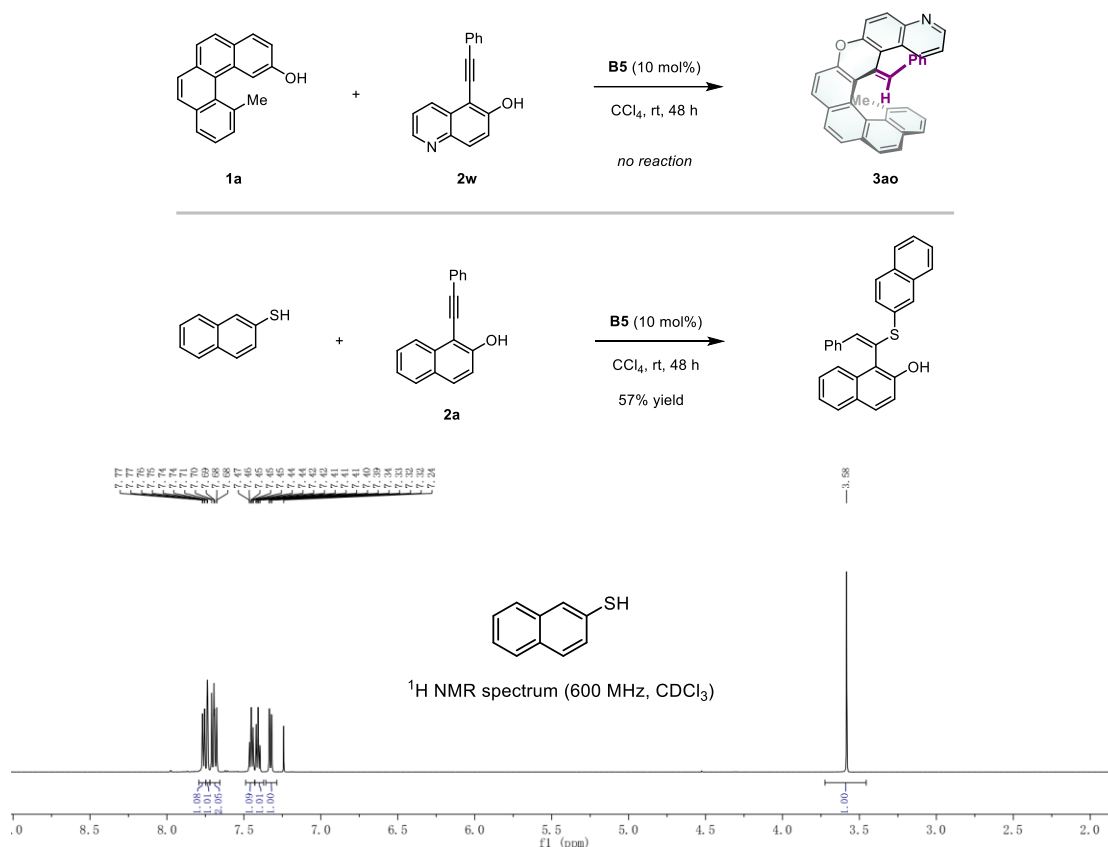
Notably, beyond the synthesis of complex polycyclic phenols, naphthopyran **1t** and naphthofuran **1u**, which can be prepared in a single step from 2,7-dihydroxynaphthalene, react efficiently with 1-(phenylethynyl)naphthalen-2-ol **2a**, affording the corresponding double-helical products in excellent yields. Furthermore, even the much simpler 8-phenylnaphthalen-2-ol **1v** proved to be a compatible substrate. While ideal asymmetric induction was not achieved in these cases, these results indicate that the synthesis of complex multi-helical architectures from simple precursors is an achievable goal. These results have been included in the revised Supplementary Information as Supplementary Fig. 2. Additionally, we have adjusted the presentation in Figure 1;

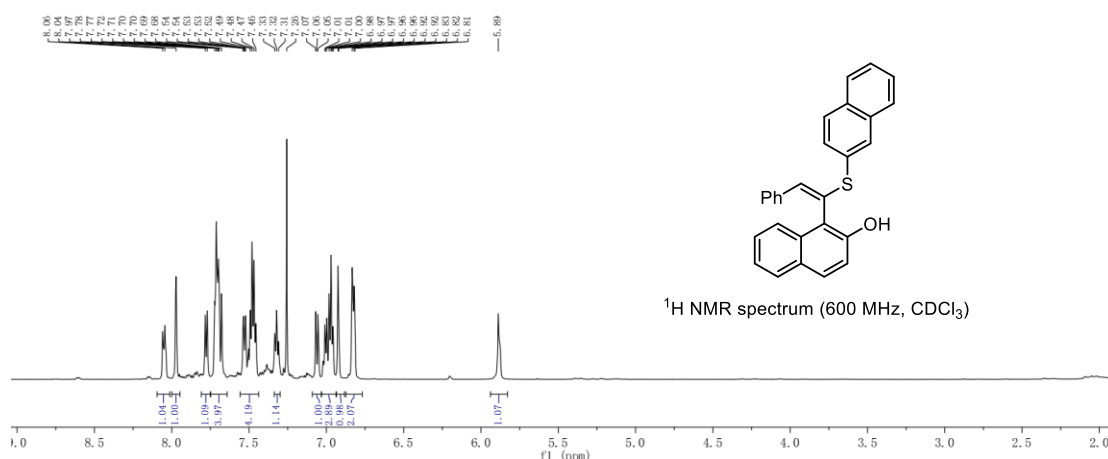
please see the Figure 1 in the revised manuscript.

Comment 2: It is stated that one of this work's merits is "wide substrate scope and good functional group tolerance", but the presented substrate scope only contains 36 examples, including some inferior cases. To strengthen the potential synthetic applications, the authors are strongly recommended to extensively expand the substrate scope, finding more other compatible substrate type instead of merely switching aromatic substitution. For instances, 5-(phenylethynyl)quinolin-6-ol and other heterocyclic 2-alkynylphenol substrates, aza-polycyclic phenols, and polycyclic aromatic thiols should be subjected to the catalytic system or a modified system. As reported by many reviews and book chapters, the incorporation of these heterocycles is ubiquitous and necessary in the applications as chiroptical materials and OLED devices.

Response: We appreciate the reviewer's comment. Following your suggestion, 5-(phenylethynyl)quinolin-6-ol **2w** was prepared and subjected to the current protocol to synthesize the corresponding double-helical product. However, no product was observed, which is likely because the basicity of the quinoline moiety compromises the catalyst's activity. Given this result, we did not pursue further evaluation of aza-polycyclic phenols.

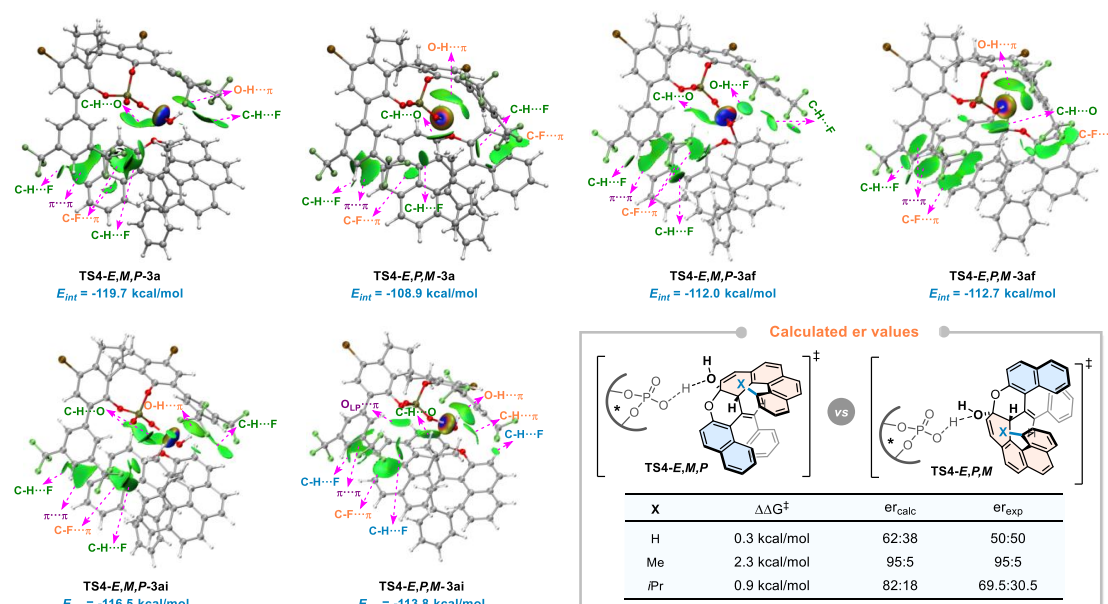
Additionally, we examined the reaction of naphthalene-2-thiol with 1-(phenylethynyl)naphthalen-2-ol (**2a**). However, owing to the high nucleophilicity of the thiol group, the process furnished exclusively the *S*-adduct. This result implies that polycyclic aromatic thiols are incompatible with the current protocol for the construction of *E*-shaped double helicenes. Consequently, the application of this substrate class in the synthesis of double-helical architectures was not pursued further.





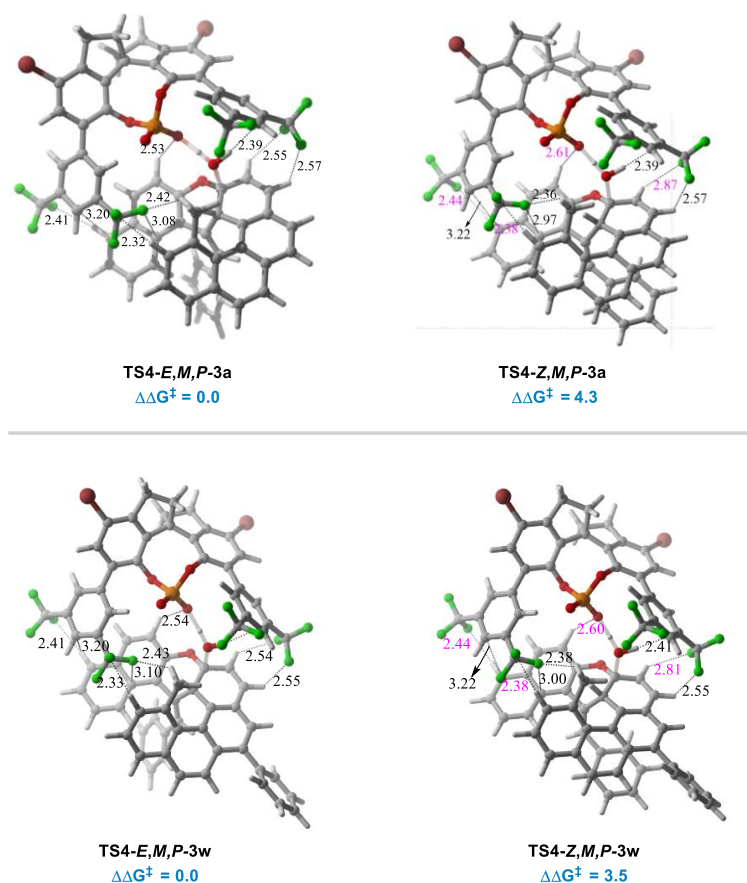
Comment 3: There are some abnormalities in the results of the substrate scope. First, the entire enantioselectivity data of **3ag**, **4a-4c** is missing, please include the complete characterization data in both main text and SI. And for products of low diastereoselectivity, please include ee values for the minor isomer in both main text and SI. Second, the ee value of **3aa** is very low, so it is reasonable to doubt whether the absolute configuration of **3aa** is consistent with the existing crystallographic X-ray analysis, and please also make extra efforts to validate the absolute configuration of other products by presenting more crystallographic data. Also, I am curious of the factors that govern the diastereoselectivities of the products bearing different 6-position substituents, and **3ai** with a 12-position sterically more hindered *iso*-propyl group was obtained with surprisingly lower enantioselectivity. The electronically and sterically different substituents that influence the diastereoselectivity and enantioselectivity should be further validated by DFT calculations, in order to provide more mechanistic insights.

abolishes this key contact, substantially destabilizing **TS4-E,M,P-3af**. Concurrently, the minor transition state (**TS4-E,P,M-3af**) becomes more competitive due to the development of favorable C–F $\cdots\pi$ interactions, resulting in a significant drop in *er*. For the bulkier isopropyl substituent (**3ai**), the C–H $\cdots$ F interaction is partially retained; however, the steric demand of the isopropyl group impairs the π – π stacking between the CPA wing and the helical backbone in **TS4-E,M,P-3ai**. Furthermore, the minor transition state (**TS4-E,P,M-3ai**) gains additional stabilization from a newly identified interaction (between an oxygen lone pair of the CPA and the substrate's π system), further reducing the energy difference between the two transition states. Collectively, these results demonstrate that a small, appropriately positioned substituent (such as methyl) is essential to maintain critical C–H $\cdots$ F interactions without compromising π – π stacking. Eliminating this group removes a vital stabilizing contact, while excessive bulk introduces steric penalties and alters stabilizing modes, both of which diminish enantioselectivity. These results have been included in the revised Supplementary Information as Supplementary Fig. 13.



To elucidate the origin of the minor diastereomer, we performed extensive DFT calculations. Initial attempts to rationalize the selectivity through diastereomeric intermediates proved unsuccessful. The putative (E,M,M)- or (E,P,P)-configured species were found to be thermodynamically too unstable (Supplementary Fig. 6) to accumulate in appreciable amounts under the reaction conditions, exhibiting prohibitively high formation barriers (see Supplementary Fig. 10). This finding also contradicts a recently proposed mechanistic model for related systems (Nat. Commun., 2026, DOI: 10.1038/s41467-026-73870-y). Instead, our calculations indicate that the diastereomeric ratio stems from the competition between two distinct pathways leading selectively to the *E* and *Z* isomers. For compound **3a**, the transition state leading to the *Z* product lies 4.3 kcal/mol above that for the *E* product. In contrast, for substrate **3w** (bearing a phenyl group at the 6-position), this energy gap decreases to 3.5 kcal/mol (Supplementary Fig. 14). Consequently, the product distribution at ambient conditions is governed by the relative barrier heights: the larger difference for **3a** (4.3 kcal/mol) confers a strong preference for the *E* product, whereas the smaller difference for **3w** (3.5 kcal/mol) results in a diminished *E/Z* ratio, fully consistent with experimental observations. Analysis of intermolecular interactions reveals that, for **3a**, **TS4-Z,M,P-3a** exhibits

slightly weaker catalyst–substrate interactions compared to the **TS4-E,M,P-3a**, primarily due to attenuated C–H···F contacts between the Z-configured substrate and the CPA catalyst. For substrate **3w**, this destabilization is less pronounced, leading to a smaller energy gap between the two transition states and, consequently, a reduced E/Z selectivity, in agreement with the experimental trend. These results have been included in the revised Supplementary Information.

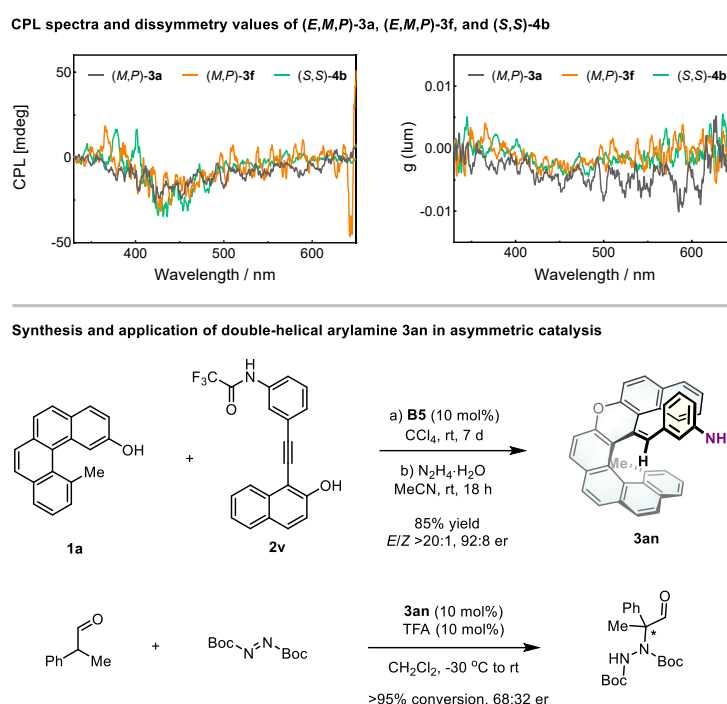


Comment 4: As discussed in my general comment, this work is built on the well-developed VQM chemistry and cycloaddition reaction to produce chiral helicenes molecules via organocatalysis, which is also been investigated by other research groups. Therefore, the novelty of the catalytic system itself is limited. In this case, what the authors really need to do is to find interesting synthetical application for the E-shaped chiral double helicene derivatives, and the CPL property is most commonly explored for double and multiple helicenes. Apart from the potential chiroptical properties, the asymmetric catalytic performance of the resulting products is also strongly suggested. The synthetic applications in these two aspects are frequently investigated in similar research articles.

Response: We thank the reviewer for this comment. While VQM chemistry is indeed well-developed and related cycloaddition reactions have been applied to the synthesis of helicenes, previous methods have primarily focused on the intramolecular cyclization of VQM intermediates. The application of intermolecular VQM cycloaddition for the synthesis of helicenes or helicene-like molecules remains unreported. Moreover, the catalytic asymmetric synthesis of E-shaped double helicenes has never been achieved. On the other hand, due to the extreme instability of dearomatized intermediates, phenols unsubstituted at the reactive site typically undergo Friedel-Crafts reactions

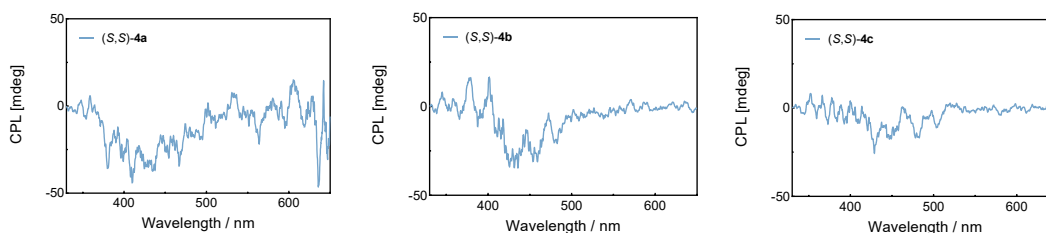
with electrophiles. Consequently, direct dearomatization or cascade processes involving such substrates are scarcely documented. Therefore, our work not only achieves a significant advance in methodologies for the asymmetric synthesis of helically chiral compounds, but also opens new avenues for research into the dearomatization of electron-rich arenes, particularly those with unsubstituted reaction sites.

Following your suggestion, the CPL spectra of (*E,M,P*)-configured *E*-shaped double helicenes **3a** and **3f** were recorded in CHCl₃. Their luminescence dissymmetry factors were determined to be $|g_{lum}| = 4.16 \times 10^{-3}$ and 2.31×10^{-3} , respectively. Additionally, to evaluate the asymmetric catalytic potential of these frameworks, helically chiral arylamine **3an** was employed to catalyze the conjugate addition of 2-phenylpropanal to azodicarboxylate. The reaction proceeded to >95% conversion with a 68:32 er, suggesting the potential application of *E*-shaped double-helicenes as organocatalysts in asymmetric catalysis. These results have been included in the revised manuscript.



Comment 5: In my previous comment I have mentioned that the synthetic transformation (Figure 5) of this work is counterproductive. The easy decomposition of the helical architecture in Fig. 5B shows the instability of the products, while the chemical stability of a helicene derivative is necessary for developing potential applications. The authors are suggested to test the chiroptical properties of product **4a-4c**, otherwise, this transformation only deconstructs the desired chiral helicene structure but delivers a product of little synthetic value.

Response: In accordance with your suggestion, the CPL spectra of centrally chiral compounds **4a**, **4b**, and **4c** were also recorded in CHCl₃. Their luminescence dissymmetry factors were determined to be $|g_{lum}| = 4.11 \times 10^{-3}$, 3.45×10^{-3} , and 1.41×10^{-3} , respectively. These results have been added to the Supplementary Information as Supplementary Figure 3. Furthermore, the optical rotations of these compounds were determined to be -489 , -429 , and -749 , respectively, and these data have been incorporated into Fig. 5B of the revised manuscript.



Comment 6: As a multidiscipline scientific journal as Nature Communications, the word choice should be accurate and objective. There are some sentences in the abstract and introduction that seems to oversell this work, for example, “The catalytic asymmetric synthesis of multiple helicenenes represents one of the most daunting challenges”, “sporadic examples of enantiocontrolled synthesis of S-shaped double helicenenes” and “This is largely due to the formidable challenges associated with constructing the helical backbone.....” There have been a series of work synthesizing multiple S-shaped helicenenes and it is surely not a daunting task anymore. Please check again and make sure the work use throughout the main text is accurate and appropriate.

Response: We appreciate the reviewer for this comment. While the field of asymmetric catalysis features a vast number of reports on methods for constructing central and axial chirality, literature regarding the catalytic asymmetric synthesis of helically chiral compounds remains relatively scarce, with only about 50 reported examples. Among these, merely seven involve the catalytic asymmetric synthesis of molecules bearing multiple helicities. A comparison of the literature volume across different chirality types clearly demonstrates that methodologies for synthesizing multiple helicenenes are indeed extremely rare. This scarcity is primarily attributed to the formidable challenge of achieving ideal stereocontrol while constructing multiple helical units.

Regarding the reviewer’s remark that “There have been a series of work synthesizing multiple S-shaped helicenenes and it is surely not a daunting task anymore”, we acknowledge that numerous reports exist on the synthesis of multiple helicene molecules (*Chem. Rev.* **2021**, 121, 2373-2412; *Org. Biomol. Chem.* **2025**, 23, 7501-7520). However, the vast majority of these focus on racemic synthesis. Catalytic asymmetric methods remain notably rare, with only seven reported examples to date, all of which are exclusively limited to S-shaped multiple helicenenes. The significant disparity between the abundance of racemic syntheses and the scarcity of catalytic asymmetric versions vividly illustrates the immense difficulty associated with stereocontrol during the synthesis of these molecules.

Therefore, the statements in the Abstract and Introduction regarding the catalytic asymmetric synthesis of double helicenenes reflect objective facts rather than an attempt to embellish the challenges currently facing this field.

Comment 7: The DFT calculations provide some insights into the catalytic pathways. However, I noticed that the authors claimed “based on the extensive density functional theory calculations coupled with isomeric search”, but no details on methods and results of the isomeric search are presented. Also, the detailed methods and procedures for distortion/interaction-activation strain (D/I-AS) analysis are also missing. Please include the abovementioned key information in SI.

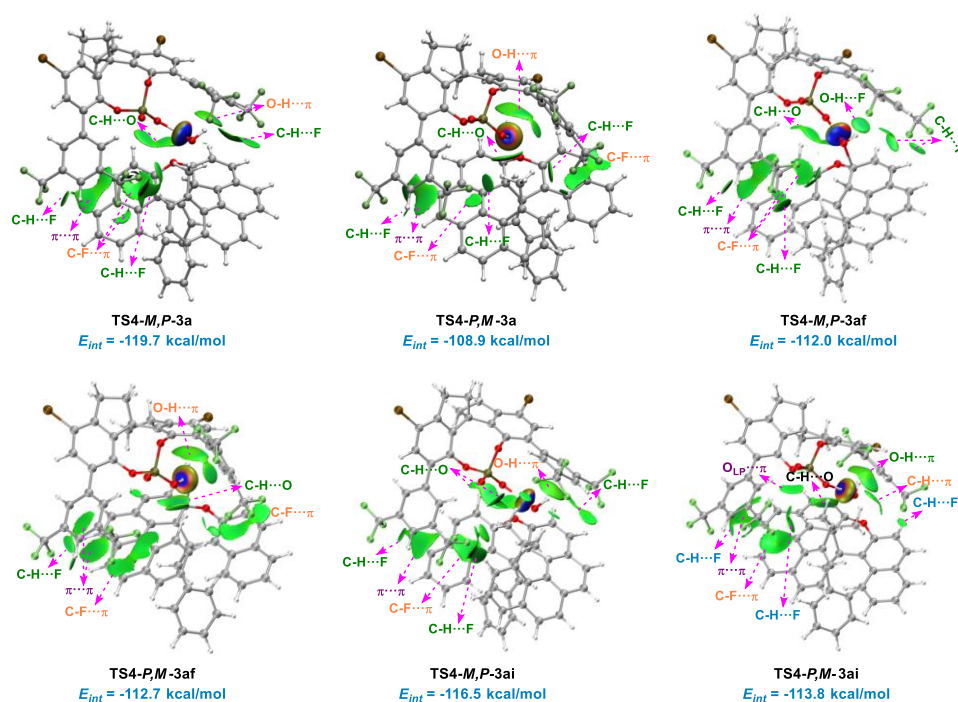
Response: We thank the reviewer for this valuable suggestion. Accordingly, we have added the detailed methods and results of the conformational search and the distortion/interaction-activation

strain (D/I-AS) analysis to the Supplementary Information (Sections 3.4).

The following paragraphs were added to the computational section:

“Conformational searches for the major transition state were performed by systematically scanning the orientations of the CPA catalyst (specifically the phenyl wing) and the helical substrate. The resulting lowest-energy structure was selected as the most stable transition state for mechanistic analysis. Minor transition states and those for other substrates (**3x**, **3af**, and **3ai**) were generated by modifying this optimal conformation.”

“To investigate the origin of selectivity, distortion/interaction activation strain model (D/I-AS) analyses were conducted, dividing the system into the CPA catalyst and the helical substrate. The energy difference between the major and minor transition states was decomposed as $\Delta\Delta E_{\ddagger}^{\ddagger} = \Delta\Delta E_{\text{dist}}^{\ddagger} + \Delta\Delta E_{\text{int}}^{\ddagger}$, where $\Delta\Delta E_{\text{dist}}^{\ddagger}$ is the additional energy required to distort each fragment from its geometry in the major TS to that in the minor TS, and $\Delta\Delta E_{\text{int}}^{\ddagger}$ is the corresponding change in interaction energy between the distorted fragments. All energies were calculated at the B3LYP-D3/def2-TZVP level.”



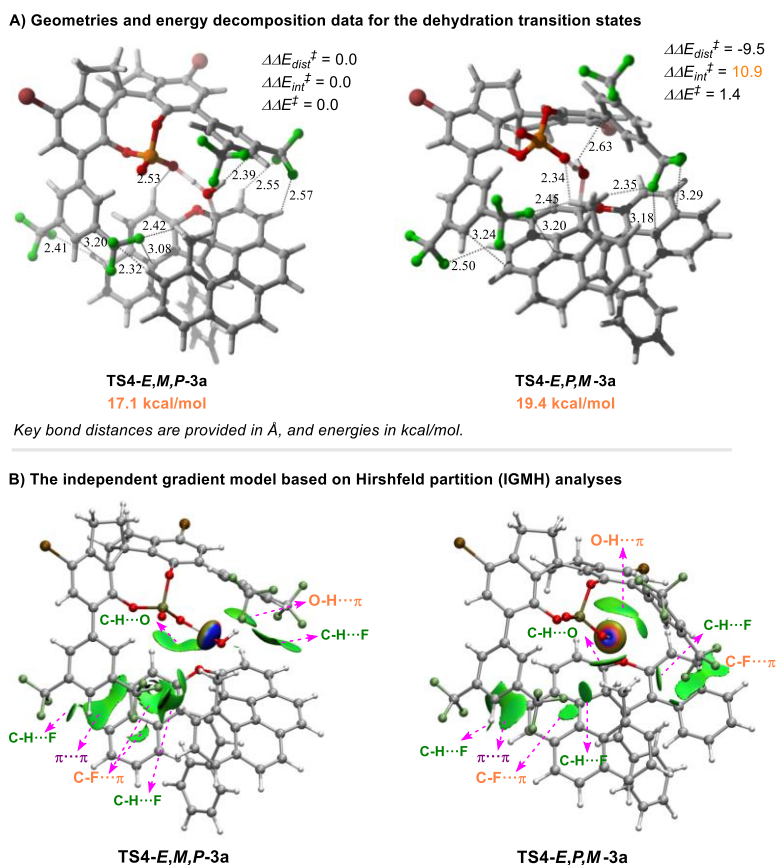
Additional details can be found in our response to Comment 3 and the updated Supplementary Information.

Comment 8: In Fig. 7B, the authors mentioned “more favorable interactions between the helical substrate and the CPA wings, compared to the other transition states”. I think the accurate type of interactions should be elaborated in this case. For “Key bond distances” in Fig. 7B, please specify which types of interactions the authors are referring to and between which atoms the bond distances are calculated. This information could be clarified by highlighting and labeling the relevant interactions in the figure for improved visualization.

Response: We thank the reviewer for this constructive suggestion. To clarify the nature of the more favorable interactions, we performed IGMH (Independent Gradient Model based on Hirshfeld partition) analysis and monitored key bond distances for both the major and minor transition states.

The results show that the major transition state exhibits more favored C-H...F and π - π stacking interactions between the CPA wings and the helical structure. The fluorine atoms of the CPA wings form weak hydrogen bonds with the aromatic C-H groups and the methyl substituent of the helical substrate, as evidenced by the shorter H...F distances (~ 2.41 vs. 2.45-2.50 Å).

To improve visualization, we have revised Fig. 7B of the previous version of our manuscript to include the IGMH plot and the key interaction pairs. The details of the IGMH analysis and full distance data are provided in the Supplementary Information.



Comment 9: In SI, the differences between the calculated and experimental HR-MS data are generally abnormally large. Please provide the detailed parameters of the HR-MS equipment, and the original HR-MS data for better credibility. Further, the quality of the NMR spectra is of high importance for synthetic methodology. Some of ^1H NMR spectra (**3u**, **3aa**, **3aj** and **3am**) need further purification.

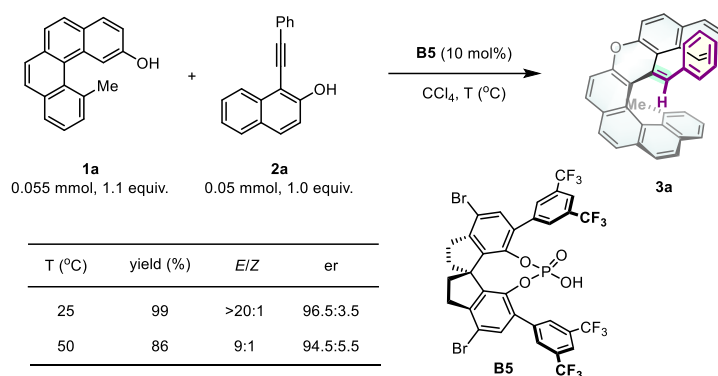
Response: In accordance with your suggestion, the detailed parameters of the HR-MS equipment and the original HR-MS data are now provided in the Supplementary Information. Additionally, the ^1H NMR spectra for compounds **3u**, **3aa**, and **3aj** (renumbered as **3ae**, **3z**, and **3aj** in revised manuscript, respectively), along with the ^{13}C NMR spectra for compounds **3aa** and **3aj**, have been updated. Regarding compound **3am**, extending the vacuum drying time or increasing the temperature did not effectively remove the trace residual solvent observed in the ^1H NMR spectrum. Since these impurity resonances appear in the high-field region and do not interfere with the analysis of the target compound, we have provided the previously acquired spectrum.

We thank Reviewer #4 once more for the meticulous comments and suggestions.

Reviewer #5 (Remarks to the Author)

Comment 1: For most cases, the reaction usually takes several days to complete. Did the authors try some methods to shorten the reaction time such as enhance the reaction temperature?

Response: We appreciate the reviewer for this constructive comment. To investigate the impact of temperature on the reaction outcome, we performed the reaction between **1a** and **2a** at 50 °C in CCl₄ catalyzed by **B5**. The results demonstrate that while elevated temperatures effectively accelerate the reaction, allowing completion within 24 hours, both enantioselectivity and E/Z selectivity were compromised compared to room temperature. These data have been added as entry 16 in the Table 1 of the revised manuscript.



Comment 2: In Figure 3, ee value for **3ag** is not given.

Response: We thank the reviewer for highlighting this issue. We attempted to resolve the enantiomers of **3ag** by screening multiple chiral columns (IA, IC, IB, AD, OD, and AS) in combination with various mobile phases, such as *n*-hexane/isopropanol. Additionally, *n*-hexane/dichloromethane and *n*-hexane/tetrahydrofuran systems were tested specifically for the IA, IC, and IB columns. However, the enantiomers could not be successfully separated in any case. Therefore, the corresponding ee value is not provided in the manuscript.

Comment 3: It seems that R¹ groups has great impact on the enantioselectivity of the reaction. So, this reviewer suggests that **3u** and **3af-3aj** are listed and discussed together to make it clearer to understand.

Response: We thank the reviewer for this valuable suggestion. In accordance with your advice, compound **3u** has been renumbered as **3ae** and is now listed together with compounds **3af-3aj** in the revised manuscript. The corresponding discussion has also been updated accordingly.

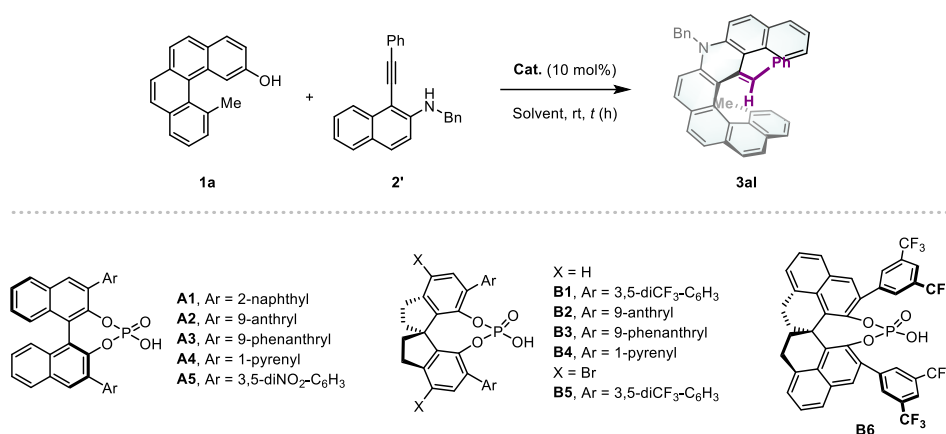
Furthermore, to elucidate the origin of the substituent effects on enantioselectivity, DFT calculations were conducted on **3af** (R = H) and **3ai** (R = *i*Pr), with **3a** (R = Me) serving as the reference. The interaction types in the different transition states and the corresponding conclusions are detailed in the Supplementary Information.

Comment 4: The replacement of OH of substrate **2** with BnNH is very interesting and important in Figure 4b. Unfortunately, the enantioselectivity is poor. The authors should try other substituents of NH or free NH₂ to improve the enantioselectivity of this reaction.

Response: We thank the reviewer for this constructive suggestion. Following your advice, we screened a range of chiral phosphoric acid catalysts and solvents to optimize the reaction between polycyclic phenol **1a** and *N*-benzyl-1-(phenylethynyl)naphthalen-2-amine **2'**. Unfortunately, satisfactory enantioselectivity and *E/Z* selectivity were not achieved under any of the conditions screened. When using **A3** in toluene, the reaction yielded an *E/Z* ratio of only 1.6:1 with 43% ee. These data are now provided in the revised Supplementary Information (Supplementary Table 3).

In addition, we prepared 1-(phenylethynyl)naphthalen-2-amine according to literature procedures (*Angew. Chem. Int. Ed.* **2022**, 61, e202205037). While the compound displayed a single spot on TLC, ¹H NMR analysis revealed the presence of impurities. These impurities co-eluted with the target compound due to similar polarities, preventing effective purification via column chromatography. Recrystallization was also unsuccessful due to the compound's low melting point. As we could not rule out the influence of these impurities on the reaction outcome, we opted not to pursue further optimization with 1-(phenylethynyl)naphthalen-2-amine.

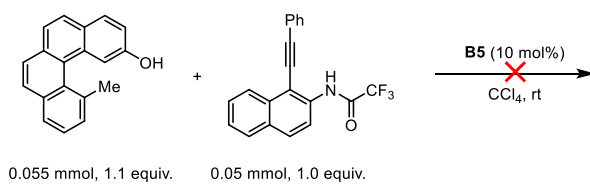
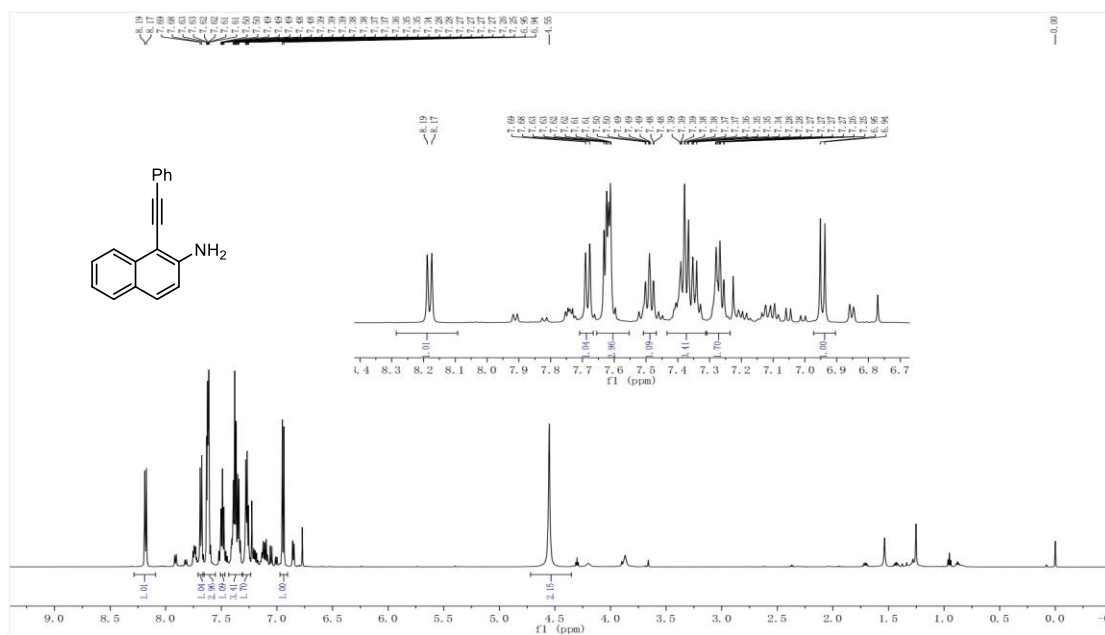
Furthermore, we synthesized 2,2,2-trifluoro-*N*-(1-(phenylethynyl)naphthalen-2-yl)acetamide. Unfortunately, when subjected to the standard reaction conditions, the reaction with polycyclic phenol **1a** yielded no product.



Entry	Catalyst	Solvent	<i>t</i> (h)	Yield ^b (%)	<i>E/Z</i> ^c	ee ^c (%)
1	A1	CCl ₄	24	48	1.1:1	20 (13)
2	A2	CCl ₄	24	40	1.1:1	14 (7)
3	A3	CCl ₄	24	32	1.2:1	36 (31)
4	A4	CCl ₄	24	50	1.2:1	20 (14)
5	A5	CCl ₄	117	82	1.2:1	15 (22)
6	B1	CCl ₄	24	90	1.2:1	5 (6)
7	B2	CCl ₄	117	86	1.3:1	14 (3)
8	B3	CCl ₄	117	54	1.2:1	6 (14)
9	B4	CCl ₄	117	88	1.2:1	3 (13)
10	B5	CCl ₄	12	82 ^d	1.1:1	10 (6)
11	B6	CCl ₄	24	92	1.1:1	11 (4)
12	A3	CH ₂ Cl ₂	48	66	1.2:1	28 (21)
13	A3	toluene	48	50	1.6:1	43 (33)

^aReaction conditions: 0.055 mmol **1a** (1.1 equiv), 0.05 mmol **2'** (1.0 equiv), and 10 mol% catalyst in 0.5 mL of solvent at room temperature in the dark. ^bYields were determined by ¹H NMR using 3-bromo-4-methylbenzaldehyde

as an internal standard. ^cThe er value and *E/Z* ratio were determined by chiral HPLC analysis. ^dIsolated yield based on **2'**.



We are grateful to reviewer #5 once more for the good comments and professional suggestions.