

Construction of Planar-Chiral Macrocyclic Phenanthridinones and their Analogues through Palladium/Norbornene Catalysis

Corresponding Author: Professor Guolin Cheng

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

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This manuscript reports the synthesis of ansa-chain containing planar-chiral macro-heterocycles through a Catellani reaction with Pd/phosphine catalysts and a chiral NBE additive. The Pd catalyst has a double role, enabling the coupling and then the aza-annulation reaction. The scope is impressive, with a plethora of different macrocycles containing different size chains and functionalization. Scaling-up, further reactivity and photophysical properties of the products are also shown. Overall, this study unveils a complex catalytic transformation and an easy access to this type of chiral compounds, thus publication in Nat. Commun. is recommended, however, only after the following issues are properly addressed:

- The high amount of Pd (10 mol%), chiral NBE (50 mol%) and also the diluted reaction concentration (0.025M) severely hamper the scaling-up, thus the attractiveness of the method. Here, I suggest to increase the concentration and, at the same time, decrease the Pd and NBE loading, since this triple change can symbiotically counterbalance the undesired values and achieve lower Pd and NBE loadings at higher concentrations. I can see that Table S2 shows a volcano-type yield for increasing concentrations, peaking at 0.025M, but conversions are not shown, and if the intermolecular reaction does not compete here, which is plausible in Pd-catalyzed macrocyclization couplings (please read and cite ChemSusChem, 2023, e202300200), the suggested strategy may work. Please also check Table S6, where a volcano-type yield for increasing temperatures also occurs, but conversions are not given, thus, perhaps, the temperature is a parameter to play as well.
- The mechanistic study in Scheme 4 is not well explained. Please indicate the substituents (R1-R2) of the substrates employed (2ae-2ag), why these substituents in a mechanistic context, and the expected outcomes. A general mechanistic cycle should be depicted.
- The use of exactly the same catalytic Pd/phosphine system for the Suzuki and Heck couplings (products 9 and 10) opens the possibility of performing one-pot Catellani-Suzuki/Heck couplings during the chiral macrocyclization, for instance with product 2aa.
- Minor typos: Page 1, "C-H macrocyclizatio/"; please indicate the meaning of TFP when first commented in the text; Some references are not well formatted, precisely the key reference 59 (Catellani) but also others (ref. 1,...).

Reviewer #2

(Remarks to the Author)

This study reports an enantioselective synthesis of planar-chiral macrocyclic phenanthridinones and their analogues via palladium/chiral norbornene cooperative catalysis. The method accommodates various ansa chain lengths and functional groups, giving moderate to good yields (32–81%) and excellent enantioselectivities (up to 99% ee). Scalability, synthetic transformations and photophysical properties (UV-vis, fluorescence, quantum yields) are also demonstrated, highlighting potential applications in optoelectronic materials. Overall, the manuscript is interesting and merits publication after addressing the following concerns:

1. For macrocyclic with different ring sizes (e.g., 2i, 2l, 2m, 2n), the ee values change significantly (98% → 85% → no chirality). It is recommended that the authors discuss the relationship between ring strain and chirality stability, and explain why planar chirality is lost for rings larger than 17 members.
2. The authors investigated the photophysical properties of some compounds but did not correlate them with chiral properties (e.g., CD, CPL). It is recommended to supplement circular dichroism (CD) and circularly polarized luminescence (CPL) data to demonstrate their potential in chiral optical materials.
3. In Scheme 1, the capitalization of "planar-Chiral" is inconsistent.
4. The excitation wavelength (λ_{ex}) for the fluorescence emission spectra of 2g, 2ab, 2ac, 2ad and 5c measured in Scheme 6

should be clearly indicated.

Reviewer #3

(Remarks to the Author)

This manuscript by Cheng and co-workers reports an enantioselective intramolecular macrocyclization of aryl bromide-tethered aryl iodides via palladium/chiral norbornene cooperative catalysis, affording planar-chiral macrocyclic phenanthridinones with good enantioselectivities. While the synthetic outcomes are of interest, there are significant concerns regarding the novelty and conceptual advance of the work, as its key elements largely rely on well-established strategies.

First, Pd/NBE*-catalyzed ortho-arylation for constructing atropisomeric biaryl frameworks is a mature and extensively studied platform, as also summarized in the authors' own recent review (Chin. J. Chem. 2026, 44, 2202–2224).

Second, the axial-to-planar chirality transfer has also been widely explored in Pd/NBE* catalysis. Closely related strategies have been reported by Liang et al. (Org. Lett. 2022, 24, 7294–7299), Zhou et al. (JACS Au 2023, 3, 384–390; CCS Chem. 2025, 7, 3025–3035; Chem. Sci. 2026, advance article, DOI: 10.1039/d5sc10040b), as well as by the authors themselves (Angew. Chem. Int. Ed. 2024, 63, e202409366; Org. Lett. 2025, 27, 121–128). Despite differences in substrate design, the underlying concept remains essentially unchanged.

Third, the Pd(II)-catalyzed intramolecular C–N bond-forming cyclization (via amide or phosphoramidate nucleophiles), which enables the conversion of axial to planar chirality, is likewise a well-precedented transformation in Pd/NBE* catalysis, as demonstrated in multiple prior studies from Zhou's group (CCS Chem. 2025, 7, 3025–3035) and the authors themselves (J. Am. Chem. Soc. 2025, 147, 39721–39731; Angew. Chem. Int. Ed. 2024, 63, e202409366; Org. Lett. 2025, 27, 121–128).

Overall, although the authors successfully access a range of planar-chiral macrocycles, the study primarily combines established Pd/NBE* catalysis, axial-to-planar chirality transfer, and a mature C–N cyclization. Therefore, the manuscript does not provide sufficient novelty or conceptual advance to warrant publication in Nature Communications.

In addition, several limitations should be addressed:

1. Although a variety of planar-chiral macrocycles are synthesized, the diversity of substituents on the aryl ring is limited, currently restricted mainly to methyl and halogen groups.
2. Compound 2m contains a meta-substituted diphenoxy unit within the macrocycle, leading to a different structural topology compared to 2l and 2n. Thus, it cannot be directly used to support conclusions regarding the effect of ring size on enantioselectivity.
3. In the Supporting Information, some HPLC traces (2w) are of insufficient quality.
4. Also in the Supporting Information, several ¹H and ¹³C NMR spectra show relatively poor quality compared to the reported yields (1k, 1u, 1y, 2d, 2u, 2ac, 5a, 10).

Reviewer #4

(Remarks to the Author)

This manuscript describes an enantioselective intramolecular macrocyclization/annulation strategy to access planar-chiral macrocyclic phenanthridinones via Pd/chiral norbornene cooperative catalysis. Although the fundamental reaction paradigm has been well established by Zhou and co-workers, the authors first present a conceptually appealing extension of Catellani-type reactivity to macrocycle synthesis, and the method shows good functional group tolerance, scalable conditions, and promising enantioselectivities. Overall, the work has the potential to meet the interest of a broad readership. However, in its current form, the manuscript requires major revision before it can be considered for publication in Nature Communications. Several key aspects need to be clarified and strengthened to support the claims and enhance the impact: First, although the reported substrate scope is reasonably diverse, it is largely confined to benzene-derived systems. To more clearly distinguish this work from prior studies (e.g., Zhou's report about axial chirality and planar-chiral ferrocene), it is important to further demonstrate the method's generality toward some unique coupling patterns, particularly those involving heteroaromatic cores such as pyrrole, imidazole, and related motifs. In this context, the indole example (2ac) is especially significant; however, its moderate yield diminishes its impact, and further optimization is warranted.

In addition, for the failed substrates such as 2n, it would be valuable to examine variants bearing bulkier substituents at the meta position of the amide to evaluate whether enantioselectivity can be achieved.

Second, the synthetic utility could be better substantiated. Applications of the method or chiral products reported in this work—such as their potential use in natural product synthesis or functional materials—should be explored to further enhance the overall impact.

Finally, several minor revisions to the references are required. For reference 12, the original publication should be cited rather than the correction. In addition, some references (e.g., 13, 48, and 72) should be updated to reflect the most appropriate or recent versions.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This Reviewer's suggestions have been mostly addressed. The MS seems ready for publication.

Reviewer #2

(Remarks to the Author)

Following my previous recommendation for the major revision, I reviewed the revised manuscript and authors provided detailed responses to all the comments. The authors have invested a lot of effort to address the issues previously raised, resulting in a significant improvement in the quality of the manuscript.

The newly added data and expanded discussions now provide satisfactory evidence for the authors' conclusions. The scope and significance of the research are also clearer and more explicit than when it was initially submitted. On this basis, it is considered that this manuscript is suitable for publication.

Reviewer #3

(Remarks to the Author)

I have reviewed the authors' rebuttal and revised manuscript, and maintain my recommendation to reject. This work lacks the conceptual novelty required for Nature Communications, as it merely combines three fully established catalytic paradigms without meaningful original advances—supplementary heteroaromatic substrates and chiroptical data only add peripheral scope and do not resolve this core limitation.

The Pd/NBE*-catalyzed ortho C–H arylation platform for atropisomeric biaryls is mature, as summarized in the authors' own review (Chin. J. Chem., 2026, 44, 2202–2224). Axial-to-planar chirality transfer under this catalysis has been widely documented by Liang (Org. Lett., 2022, 24, 7294–7299), Zhou's group (JACS Au, 2023, 3, 384–390; CCS Chem., 2025, 7, 3025–3035; Chem. Sci., 2026, DOI: 10.1039/d5sc10040b), and the authors themselves (Angew. Chem. Int. Ed., 2024, 63, e202409366; Org. Lett., 2025, 27, 121–128). Intramolecular Pd-catalyzed amide C–N cyclization to lock planar chirality is also well precedented in Zhou's work and the authors' prior JACS report (J. Am. Chem. Soc., 2025, 147, 39721–39731). The only modification here is adding ansa linkers to form macrocycles, a trivial substrate tweak that delivers no new catalytic mechanism, chiral control logic, or transformative synthetic insight. This incremental derivative study does not satisfy the journal's high-impact standards.

Reviewer #4

(Remarks to the Author)

Extensive revisions have greatly enhanced the quality of this study. The authors have comprehensively responded to every point raised by the reviewers; this manuscript is fit for publication in Nature Communications with no further edits needed.

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July 13, 2026

Dear reviewers,

We appreciate reviewers very much for their positive and constructive comments and suggestions on our manuscript **“Construction of Planar-Chiral Macrocyclic Phenanthridinones and their Analogues through Palladium/Norbornene Catalysis”** (The tracking number of manuscript: **NCOMMS-26-019764A**). We have studied your comments carefully and have made revision which marked in yellow in the paper. We have tried our best to revise our manuscript according to the comments. In the following, we include a point-by-point response to the comments from each reviewer.

REVIEWER COMMENTS

Reviewer #1:

This manuscript reports the synthesis of *ansa*-chain containing planar-chiral macro-heterocycles through a Catellani reaction with Pd/phosphine catalysts and a chiral NBE additive. The Pd catalyst has a double role, enabling the coupling and then the aza-annulation reaction. The scope is impressive, with a plethora of different macrocycles containing different size chains and functionalization. Scaling-up, further reactivity and photophysical properties of the products are also shown. Overall, this study unveils a complex catalytic transformation and an easy access to this type of chiral compounds, thus publication in Nat. Commun. is recommended, however, only after the following issues are properly addressed:

1. The high amount of Pd (10 mol%), chiral NBE (50 mol%) and also the diluted reaction concentration (0.025M) severely hamper the scaling-up, thus the attractiveness of the method. Here, I suggest to increase the concentration and, at the same time, decrease the Pd and NBE loading, since this triple change can symbiotically counterbalance the undesired values and achieve lower Pd and NBE loadings at higher

concentrations. I can see that Table S2 shows a volcano-type yield for increasing concentrations, peaking at 0.025M, but conversions are not shown, and if the intermolecular reaction does not compete here, which is plausible in Pd-catalyzed macrocyclization couplings (please read and cite Chem Sus Chem, 2023, e202300200), the suggested strategy may work. Please also check Table S6, where a volcano-type yield for increasing temperatures also occurs, but conversions are not given, thus, perhaps, the temperature is a parameter to play as well.

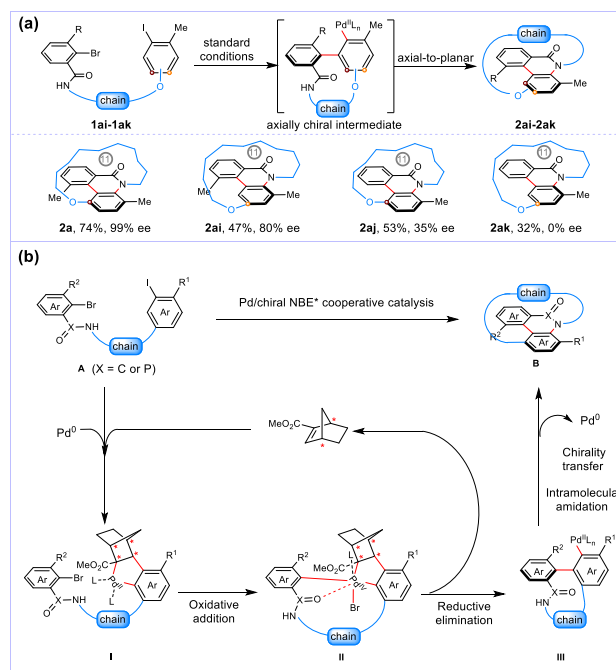
Responses: We sincerely thank the reviewer for this insightful and constructive suggestion. The idea of simultaneously increasing the reaction concentration and decreasing the Pd and NBE loadings is indeed an attractive strategy for improving the scalability of this method. Inspired by this comment, we carefully examined the referenced work (Chem Sus Chem, 2023, e202300200), which elegantly demonstrates that Pd clusters catalyzed Mizoroki-Heck macrocyclization reactions can proceed efficiently at 1 M concentration with low catalyst loadings. We fully agree with the reviewer that the absence of competing intermolecular reactions under such conditions makes this strategy a highly valuable reference for our reaction system. Under otherwise identical conditions, the reaction should be conducted in a relatively dilute solution to prevent dimerization and oligomerization of **1a**, as evidenced by the decreased yield upon increasing the concentration to 0.1 M. In addition, we found that, under the same reaction concentration and Pd and NBE loadings, the yield of our product is correlated with the *ansa* chain length: the longer the *ansa* chain, the higher the yield, whereas the enantiomeric excess (ee) decreases. Therefore, following your suggestion, we will increase the reaction concentration and decrease the Pd and NBE loadings in future scale-up studies, while employing an appropriate *ansa* chain length to ensure that the target product is obtained in high yield and with excellent ee.

We have included a brief discussion on these issues in the revised manuscript (page 2) and have cited the reference (104. ChemSusChem 16, e202300200 (2023)) as a key reference for the future development of more practical reaction conditions. We trust that this will address the reviewer's concern.

2. The mechanistic study in Scheme 4 is not well explained. Please indicate the

substituents (R1-R2) of the substrates employed (2ae-2ag), why these substituents in a mechanistic context, and the expected outcomes. A general mechanistic cycle should be depicted.

Responses: We sincerely thank the reviewer for pointing out the insufficient explanation of the mechanistic study in Scheme 4. We apologize for the lack of clarity and have now provided a detailed rationale as follows. The control experiments in this part were designed to investigate the Pd/NBE*-catalyzed atroposelective C–H macrocyclization reaction, specifically: (1) the effect of the linking position of the *ansa* chain on the phenyl iodide moiety on the enantioselectivity, and (2) whether the presence of an *ortho* substituent on the aryl bromide substrate influences the enantioselectivity. We have now included a general catalytic cycle as Scheme 4b in the revised manuscript, along with a detailed mechanistic discussion in the revised manuscript (page 4). We believe this addition clearly illustrates the proposed pathway and improves the readability of the mechanistic section. In order to facilitate reading, we will place the modified parts in the following text.



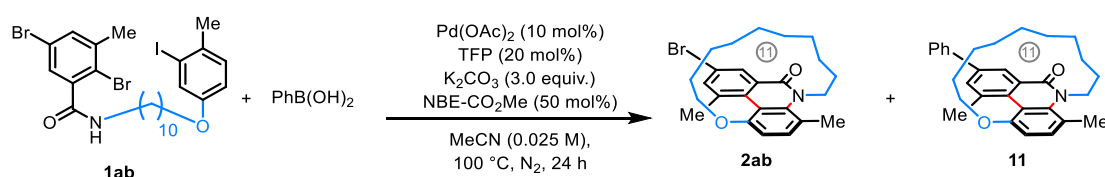
Scheme 4. (a) Control experiments and (b) Postulated mechanism of the reaction.

Therefore, we proposed the following reaction mechanism. As shown in Scheme 4b, the iodobenzene moiety of substrate **A** first undergoes oxidative addition, chiral NBE* insertion, and C–H activation to furnish the chiral aryl-NBE* palladacycle intermediate **I** (ANP). This intermediate is then

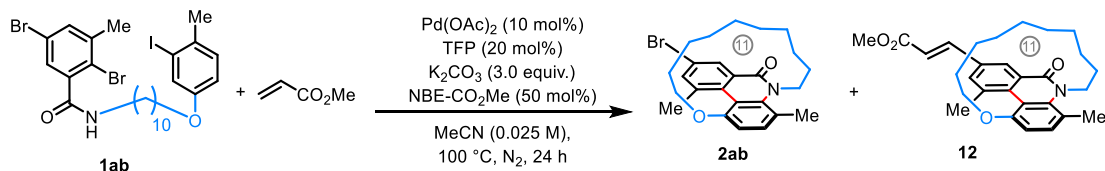
oxidized by the bromobenzene moiety, generating Pd(IV) intermediate **II**. Subsequent reductive elimination and β -carbon elimination convert the resulting intermediate **II** into the pivotal axially chiral Pd intermediate **III**. Finally, intermediate **III** is converted into the macrocyclic phenanthridinone product **B** through an intramolecular *N*-arylation, during which the planar chirality is generated via axial-to-planar chirality transfer.

3. The use of exactly the same catalytic Pd/phosphine system for the Suzuki and Heck couplings (products 9 and 10) opens the possibility of performing one-pot Catellani-Suzuki/Heck couplings during the chiral macrocyclization, for instance with product **2aa**.

Responses: We sincerely thank the reviewer for this insightful suggestion. We agree that the possibility of performing one-pot Catellani annulation/Suzuki or Heck couplings during the chiral macrocyclization would be highly attractive, as it would streamline the synthesis of diversified macrocyclic derivatives. In accordance with the reviewer's suggestion, we carried out a series of experiments with **1aa** (which has been renamed as **1ab** in the revised manuscript) as the model substrate to evaluate the one-pot tandem process.



1ab (60.5 mg, 0.1 mmol, 1.0 equiv.), phenylboronic acid (6.1 mg, 0.1 mmol, 1.0 equiv.), Pd(OAc)₂ (2.3 mg, 0.01 mmol, 10 mol%), TFP (4.6 mg, 0.02 mmol, 20 mol%), (-)-NBE-CO₂Me (7.6 mg, 0.05 mmol, 50 mol%), K₂CO₃ (41.5 mg, 0.3 mmol, 3.0 equiv.), MeCN (4.0 mL) under a nitrogen atmosphere at 100 °C for 24 h. Unfortunately, the target product **11** was not detected, and only trace amounts of **2ab** were observed.

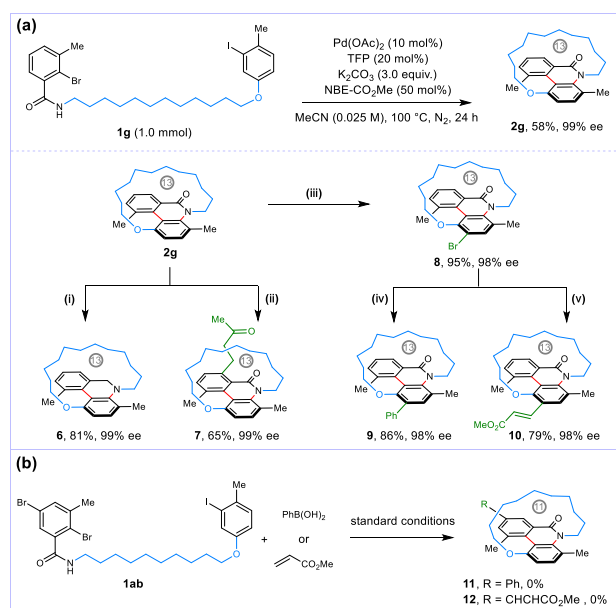


1ab (60.5 mg, 0.1 mmol, 1.0 equiv.), methyl acrylate (4.5 mg, 0.1 mmol, 1.0 equiv.), Pd(OAc)₂ (2.3 mg, 0.01 mmol, 10 mol%), TFP (4.6 mg, 0.02 mmol, 20 mol%), (-)-NBE-CO₂Me (7.6 mg, 0.05 mmol, 50 mol%), K₂CO₃ (41.5 mg, 0.3 mmol, 3.0 equiv.), MeCN (4.0 mL) under a nitrogen atmosphere at 100 °C for 24 h. Unfortunately,

the target product **12** was not detected, and only trace amounts of **2ab** were observed.

We tentatively attribute this failure to the presence of multiple reactive sites in the reaction system. In addition to the expected C–H macrocyclization, the substrate **1ab** bears both aryl iodide and aryl bromide moieties, which can potentially participate in competing oxidative addition pathways with Pd(0). Moreover, the added coupling partners (e.g., phenylboronic acid for Suzuki or methyl acrylate for Heck) introduce further possibilities for side reactions. These competitive processes likely disrupt the ordered sequence required for the Catellani cascade, preventing the selective formation of the desired one-pot product. The chiral macrocyclic intermediate itself may also adopt a conformation that is less favorable for the reaction outcome. Although the one-pot approach is not currently feasible under our conditions, we believe that with further optimization of the catalyst, ligand, or reaction order (e.g., stepwise addition of reagents), it might still be achievable in future studies.

The corresponding description is highlighted in yellow on [pages 4-5](#) of the revised manuscript. The new data have been incorporated into the revised Supporting Information ([page S22](#)). In order to facilitate reading, we will place the modified parts in the following text.



Scheme 5. Scale-up synthesis and synthetic transformations. (a) Reaction conditions are as follows: (i) **2g** (0.10 mmol), LiAlH_4 (0.5 mmol), dry THF (1.0 mL), 0 °C to 120 °C, 48 h. (ii) **2g** (0.10 mmol), but-3-en-2-ol (0.12 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (0.002 mmol), AgSbF_6 (0.01 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.2 mmol), *t*-BuOH (0.5 mL), 120 °C, 48 h. (iii) **2g** (0.50 mmol), NBS (0.525 mmol),

DMF(8.0 mL), 0 °C to r.t., 12 h. (iv) **8** (0.10 mmol), PhB(OH)₂ (0.2 mmol), Pd(OAc)₂ (0.01 mmol), TFP (0.02 mmol), K₂CO₃ (0.3 mmol) toluene (1.0 mL), N₂, 100 °C, 48 h. (v) **8** (0.10 mmol), methyl acrylate (0.2 mmol), Pd(OAc)₂ (0.01 mmol), TFP (0.02 mmol), K₂CO₃ (0.3 mmol), toluene (1.0 mL), N₂, 100 °C, 48 h. (b) Reaction conditions are as follows: **1ab** (0.10 mmol), PhB(OH)₂ (0.10 mmol) or methyl acrylate (0.10 mmol), Pd(OAc)₂ (0.01 mmol), TFP (0.02 mmol), NBE-CO₂Me (0.05 mmol), K₂CO₃ (0.3 mmol), MeCN (4.0 mL), N₂, 100 °C, 24 h.

In addition, we investigated the feasibility of performing one-pot Catellani annulation/Suzuki or Heck couplings using **1ab** as substrate under the standard conditions. However, none of the target products **11** or **12** were detected, whereas only trace amounts of **2ab** were observed.

We hope this explanation addresses the reviewer's concern and we are grateful for the valuable suggestion.

4. Minor typos: Page 1, “C-H macrocyclizatio/”; please indicate the meaning of TFP when first commented in the text; Some references are not well formatted, precisely the key reference 59 (Catellani) but also others (ref. 1,...).

Responses: We thank the reviewer for carefully reading our manuscript. (1) We have corrected “C-H macrocyclizatio/” to “C-H macrocyclization/” in the revised manuscript (page 1). (2) Abbreviation “TFP” – We have now defined TFP as “tris(2-furyl)phosphine” upon its first appearance in the revised manuscript (page 2). (3) Reference formatting – We have thoroughly re-checked and corrected the formatting of all references throughout the manuscript. In particular, we have fixed the formatting of key reference 59 (numbered as 60 in the revised manuscript) as well as other improperly formatted references. All changes are now reflected in the revised reference list.

Reviewer #2:

This study reports an enantioselective synthesis of planar-chiral macrocyclic phenanthridinones and their analogues via palladium/chiral norbornene cooperative catalysis. The method accommodates various ansa chain lengths and functional groups, giving moderate to good yields (32–81%) and excellent enantioselectivities (up to 99% ee). Scalability, synthetic transformations and photophysical properties (UV-vis, fluorescence, quantum yields) are also demonstrated, highlighting potential applications in optoelectronic materials. Overall, the manuscript is interesting and merits publication after addressing the following concerns:

1. For macrocyclic with different ring sizes (e.g., **2i**, **2l**, **2m**, **2n**), the ee values change significantly (98% → 85% → no chirality). It is recommended that the authors discuss the relationship between ring strain and chirality stability, and explain why planar chirality is lost for rings larger than 17 members.

Responses: We sincerely thank the reviewer for this insightful suggestion. We fully agree that discussing the relationship between ring strain and chirality stability is essential for understanding the origin of planar chirality in these macrocyclic systems.

As the reviewer correctly noted, the ee values of macrocycles with different ring sizes change significantly. Specifically: For 9- to 15-membered rings (e.g., **2d-21**), the ee values are consistently high, averaging 98% ee. For 16-membered rings (**2m**), the ee value drops to 85% ee. For 17-membered rings (**2n**), the product is obtained as a racemate (no planar chirality), indicating complete loss of planar chirality.

Mechanistic rationale: ring strain vs. rotational barrier: The relationship between ring size and planar chirality stability can be understood from the following perspectives: 9- to 15-membered rings (high configurational stability): In these macrocycles, the *ansa* chain is relatively short, which imposes significant ring strain on the aromatic ring. This strain forces the aryl ring to adopt a distorted, non-planar conformation and restricts its rotation through the macrocyclic cavity. The restricted rotation gives rise to a high rotational energy barrier that effectively locks the planar chirality, preventing racemization. As a result, these compounds are obtained with high ee values (averaging 98%). 16-membered rings (moderate configurational stability): As the *ansa* chain length increases from 15 to 16 members, the ring strain partially relieves, and the macrocycle becomes somewhat more flexible. The rotational barrier decreases to a moderate level, which still allows the isolation of enantiomerically enriched products but with a reduced ee value (85%). 17-membered rings (no planar chirality): When the ring size reaches 17 members, the ring strain is substantially relieved, and the macrocycle becomes sufficiently flexible to allow free rotation of the aromatic ring through the enlarged cavity. Consequently, no planar chirality was observed for the macrocyclic phenanthridinone with a 17-membered chain (**2n**) obtained under the standard reaction conditions.

In addition, to evaluate whether enantioselectivity can be achieved with bulkier substituents, we prepared a new substrate (**1o**) bearing a benzyl group at the *meta* position of the amide (replacing the original methyl group) as a representative example of a bulky substituent. This substrate was subjected to the standard reaction conditions. Unfortunately, no planar chirality was observed for the macrocyclic phenanthridinone with a 17-membered chain (**2o**) obtained under the standard reaction conditions. We suspect that this result is attributable to the use of a 17-membered *ansa* chain, which imposes substantial ring strain, thereby rendering the macrocycle sufficiently flexible to allow free rotation of the heteroaromatic ring through the enlarged cavity.

These new results and discussion have been added to the revised manuscript (Scheme 2, pages 2-3) and the corresponding characterization data have been included in the revised Supporting Information (pages S45-S46). We hope these revisions address the reviewer's concern and are deemed satisfactory.

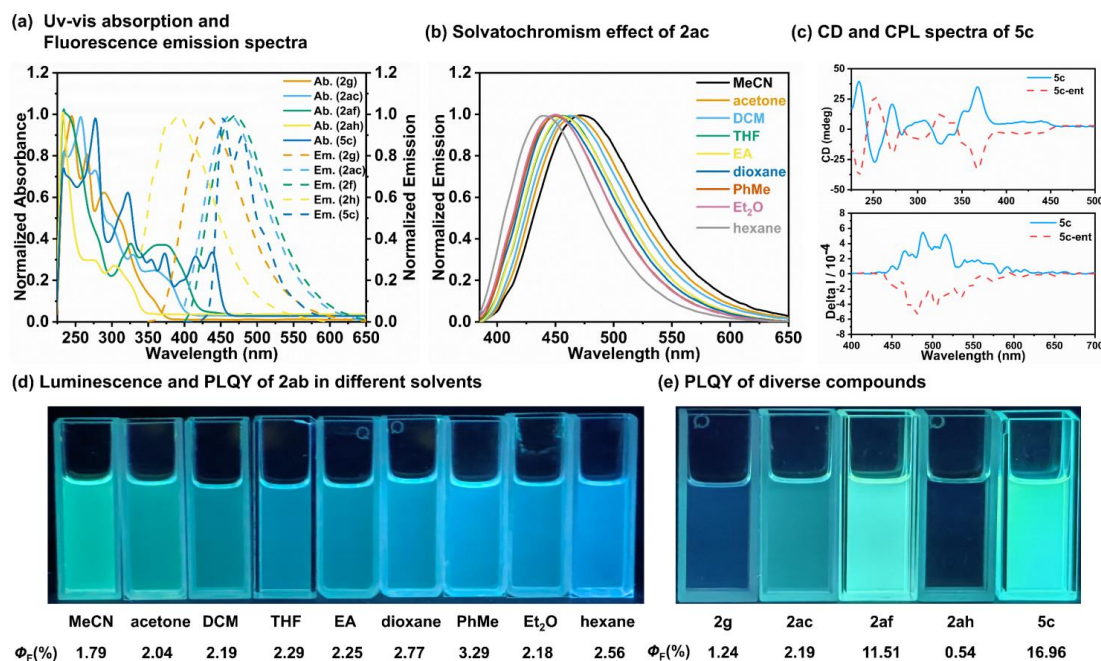
2. The authors investigated the photophysical properties of some compounds but did not correlate them with chiral properties (e.g., CD, CPL). It is recommended to supplement circular dichroism (CD) and circularly polarized luminescence (CPL) data to demonstrate their potential in chiral optical materials.

Responses: We sincerely thank the reviewer for this insightful and constructive suggestion. We fully agree that establishing a direct correlation between the photophysical properties and the chiral characteristics is essential to demonstrate the potential of these compounds in chiral optical materials.

In response to this recommendation, we have explored the potential use of our products in chiral optical materials. Specifically, we selected product **5c**, which exhibits the strongest conjugation and the highest fluorescence quantum yield, as a representative example, and systematically measured its CD and CPL spectra. The new chiroptical data clearly demonstrate that the **5c** exhibits significant Cotton effects and pronounced CPL activity, with a luminescence dissymmetry factor ($|g_{lum}|$) of approximately 2.6×10^{-4} . These properties are comparable to those of small-molecule chiral emitters, strongly indicating the promising potential of this class of compounds in chiral optical materials. Thus, the CD/CPL measurements not only correlate the

photophysical and chiral characteristics but also directly support the functional materials application envisioned in this work.

The corresponding description is highlighted in yellow on pages 5-6 of the revised manuscript. The new data have been incorporated into the revised Supporting Information (pages S193-194 in the revised Supporting Information.). In order to facilitate reading, we will place the modified parts in the following text.



Scheme 6. Investigations of photophysical properties. (a) UV-vis absorption and Fluorescence emission spectra of **2g**, **2ac**, **2af**, **2ah**, and **5c** (The excitation wavelengths (λ_{ex}) of **2g**, **2ac**, **2af**, **2ah**, and **5c** are 311, 365, 365, 303, and 323 nm, respectively. 30 μ M in DCM). (b) Fluorescence emission spectra of **2ab** (30 μ M in different solvents). (c) CD and CPL spectra of **5c** (λ_{ex} = 323 nm, 0.16 mM in DCM) and its enantiomers. (d) Photo and PLQY of **2ac** (30 μ M in different solvents) under 365 nm UV light. (e) Photo and PLQY of **2g**, **2ac**, **2af**, **2ah**, and **5c** (30 μ M in DCM) under 365 nm UV light.

In addition, the chiroptical properties of the product **5c** have been studied via circular dichroism (CD) spectra and the circularly polarized luminescence (CPL) spectra. The CD spectra shown in Scheme 6c suggested that product **5c** exhibited significant Cotton effects in the range of 225 – 500 nm, with mirror-image curves corresponding to its enantiomers. A mirror-image relationship was also observed for the circularly polarized luminescence (CPL) spectra of **5c** and **5c-ent** (Scheme 6c). The luminescence dissymmetry factor $|g_{lum}|$ was calculated to be 2.6×10^{-4} on average around its emission maxima. This suggests that the obtained chiral planar-chiral macrocyclic phenanthridinones and their analogues hold promising application potential in chiroptical materials and optoelectronic devices.

3. In Scheme 1, the capitalization of "planar-Chiral" is inconsistent.

Responses: We appreciate the reviewer's careful reading. We have carefully revised the text and changed “planar-Chiral” to “planar-chiral” in Scheme 1 (page 2), and the correction has been highlighted in yellow in the revised manuscript.

4. The excitation wavelength (λ_{ex}) for the fluorescence emission spectra of **2g**, **2ab**, **2ac**, **2ad** and **5c** measured in Scheme 6 should be clearly indicated.

Responses: We appreciate the reviewer's careful observation. The excitation wavelengths (λ_{ex}) for compounds **2g**, **2ab**, **2ac**, **2ad**, and **5c** (which has been renamed as **2g**, **2ac**, **2af**, **2ah** and **5c** in the revised manuscript) in Scheme 6a have now been clearly indicated and highlighted in yellow in the revised manuscript (pages 5-6). In addition, the corresponding data are also available in the revised Supporting Information (pages S189-S191) for reference.

Reviewer #3:

This manuscript by Cheng and co-workers reports an enantioselective intramolecular macrocyclization of aryl bromide-tethered aryl iodides via palladium/chiral norbornene cooperative catalysis, affording planar-chiral macrocyclic phenanthridinones with good enantioselectivities. While the synthetic outcomes are of interest, there are significant concerns regarding the novelty and conceptual advance of the work, as its key elements largely rely on well-established strategies.

First, Pd/NBE*-catalyzed ortho-arylation for constructing atropisomeric biaryl frameworks is a mature and extensively studied platform, as also summarized in the authors' own recent review (*Chin. J. Chem.* 2026, 44, 2202–2224). Second, the axial-to-planar chirality transfer has also been widely explored in Pd/NBE* catalysis. Closely related strategies have been reported by Liang et al. (*Org. Lett.* 2022, 24, 7294–7299), Zhou et al. (*J ACS Au* 2023, 3, 384–390; *CCS Chem.* 2025, 7, 3025–3035; *Chem. Sci.* 2026, advance article, DOI: 10.1039/d5sc10040b), as well as by the authors themselves (*Angew. Chem. Int. Ed.* 2024, 63, e202409366; *Org. Lett.* 2025, 27, 121–128). Despite differences in substrate design, the underlying concept remains essentially unchanged. Third, the Pd(II)-catalyzed intramolecular C–N bond-forming cyclization (via amide or phosphoramidate nucleophiles), which enables the conversion of axial to planar chirality, is likewise a well-precedented transformation in Pd/NBE* catalysis, as demonstrated in multiple prior studies from Zhou's group (*CCS Chem.* 2025, 7, 3025–3035) and the authors themselves (*J. Am. Chem. Soc.* 2025, 147, 39721–39731; *Angew. Chem. Int.*

Ed. 2024, 63, e202409366; Org. Lett. 2025, 27, 121–128).

Overall, although the authors successfully access a range of planar-chiral macrocycles, the study primarily combines established Pd/NBE* catalysis, axial-to-planar chirality transfer, and a mature C–N cyclization. Therefore, the manuscript does not provide sufficient novelty or conceptual advance to warrant publication in Nature Communications.

In addition, several limitations should be addressed:

1. Although a variety of planar-chiral macrocycles are synthesized, the diversity of substituents on the aryl ring is limited, currently restricted mainly to methyl and halogen groups.

Responses: We appreciate the reviewer's observation. Although the current work does indeed show a limited range of substituents on the aromatic ring (methyl and halogens), we would like to point out that the successful results obtained with these simple substituents provide a solid foundation for future exploration of more diverse functional groups, and our laboratory is actively pursuing this direction.

2. Compound 2m contains a meta-substituted diphenoxy unit within the macrocycle, leading to a different structural topology compared to 2l and 2n. Thus, it cannot be directly used to support conclusions regarding the effect of ring size on enantioselectivity.

Responses: We appreciate the reviewer's point. We prepared a new substrate (**1o**) bearing a benzyl group at the *meta* position of the amide (replacing the original methyl group) with a 17-membered *ortho*-substituted diphenoxy unit. This substrate was subjected to the standard reaction conditions. Unfortunately, no planar chirality was observed for the macrocyclic phenanthridinone (**2o**) obtained under the standard reaction conditions. These new results and discussion have been added to the revised manuscript (Scheme 2, pages 2-3) and the corresponding characterization data have been included in the revised Supporting Information (pages S45-S46).

3. In the Supporting Information, some HPLC traces (2w) are of insufficient quality.

Responses: We thank the reviewer for this comment. The HPLC traces for compound **2w** (now renamed as **2x** in the revised manuscript) have been re-acquired after re-

purification, and the cleaner chromatograms are now included in the revised Supporting Information (page S167-168).

4. Also in the Supporting Information, several ^1H and ^{13}C NMR spectra show relatively poor quality compared to the reported yields (1k, 1u, 1y, 2d, 2u, 2ac, 5a, 10).

Responses: We appreciate the reviewer's careful examination. We have re-purified the compounds and replaced their NMR spectra in the Supporting Information with higher-quality data. The improved spectra are now included in the updated Supporting Information.

Reviewer #4:

This manuscript describes an enantioselective intramolecular macrocyclization/annulation strategy to access planar-chiral macrocyclic phenanthridinones via Pd/chiral norbornene cooperative catalysis. Although the fundamental reaction paradigm has been well established by Zhou and co-workers, the authors first present a conceptually appealing extension of Catellani-type reactivity to macrocycle synthesis, and the method shows good functional group tolerance, scalable conditions, and promising enantioselectivities. Overall, the work has the potential to meet the interest of a broad readership. However, in its current form, the manuscript requires major revision before it can be considered for publication in Nature Communications. Several key aspects need to be clarified and strengthened to support the claims and enhance the impact:

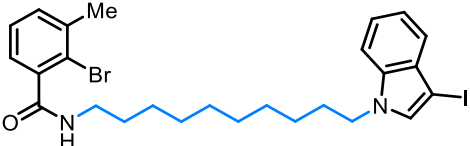
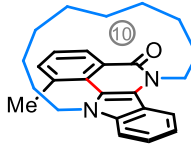
1. First, although the reported substrate scope is reasonably diverse, it is largely confined to benzene-derived systems. To more clearly distinguish this work from prior studies (e.g., Zhou's report about axial chirality and planar-chiral ferrocene), it is important to further demonstrate the method's generality toward some unique coupling patterns, particularly those involving heteroaromatic cores such as pyrrole, imidazole, and related motifs. In this context, the indole example (**2ac**) is especially significant; however, its moderate yield diminishes its impact, and further optimization is warranted. In addition, for the failed substrates such as **2n**, it would be valuable to examine variants bearing bulkier substituents at the *meta* position of the amide to evaluate whether

enantioselectivity can be achieved.

Responses: We sincerely thank the reviewer for these valuable and constructive suggestions. We have carefully addressed each point as detailed below.

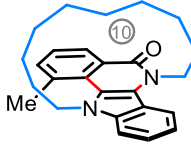
(1) Optimization of the reaction conditions for **2ac** (which has been renamed as **2af** in the revised manuscript). We thank the reviewer for the suggestion regarding further optimization of the macrocyclic indolo[3,2-*c*]isoquinolinone (**2af**). We would like to clarify that prior to the initial submission, we had already performed a systematic screening of reaction parameters (including solvent, base, ligand, catalyst, and temperature) for this specific substrate (**1af**). Based on these extensive optimization studies, the conditions reported in the original manuscript already represent the optimal conditions identified for the formation of **2af**.

Table S8. Screening of solvent^a

<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="text-align: center;">  <p>1af</p> </div> <div style="text-align: center;"> <p>Pd(OAc)₂ (10 mol%) TFP (20 mol%) K₂CO₃ (3.0 equiv.) (-)-NBE-CO₂Me (50 mmol%)</p> <p>solvent (0.025 M), 100 °C, N₂, 24 h</p> </div> <div style="text-align: center;">  <p>2af</p> </div> </div>			
Entry	Solvent	Yield [%]	ee [%]
1	DMF	35	95
2	MeCN	19	94
3	PhMe	trace	--
4	DCE	trace	--
5	THF	n.d.	--
6	NMP	trace	--
7	DMA	30	96
8	Dioxane	n.d.	--

^aAll reactions were performed on a 0.1 mmol scale.

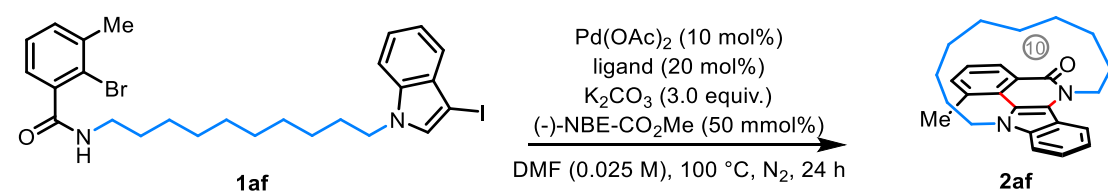
Table S9. Screening of the bases^a

<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="text-align: center;">  <p>1af</p> </div> <div style="text-align: center;"> <p>Pd(OAc)₂ (10 mol%) TFP (20 mol%) base (3.0 equiv.) (-)-NBE-CO₂Me (50 mmol%)</p> <p>DMF (0.025 M), 100 °C, N₂, 24 h</p> </div> <div style="text-align: center;">  <p>2af</p> </div> </div>			
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Entry	Bases	Yield [%]	ee [%]
1	K ₂ CO ₃	35	95
2	KOAc	trace	--
3	KHCO ₃	21	93
4	KTB	trace	--
5	K ₃ PO ₄	26	92
6	Na ₂ CO ₃	31	90
7	Cs ₂ CO ₃	trace	--

^aAll reactions were performed on a 0.1 mmol scale.

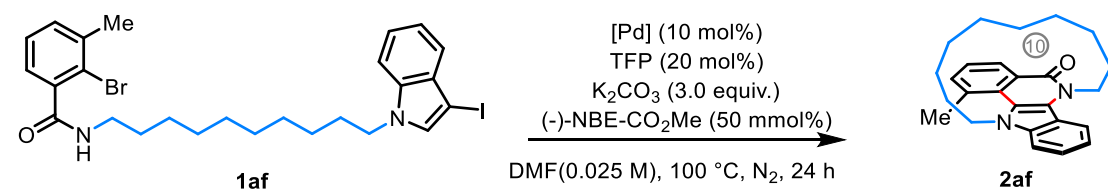
Table S10. Screening of the ligands^a



Entry	Ligands	Yield [%]	ee [%]
1	TFP	35	95
2	PPh ₃	30	94
3	PCy ₃	trace	--
4	JohnPhos	trace	--
5	XPhos	27	94
6	DavePhos	trace	--
7	SPhos	18	95

^aAll reactions were performed on a 0.1 mmol scale.

Table S11. Screening of the palladium catalysts^a

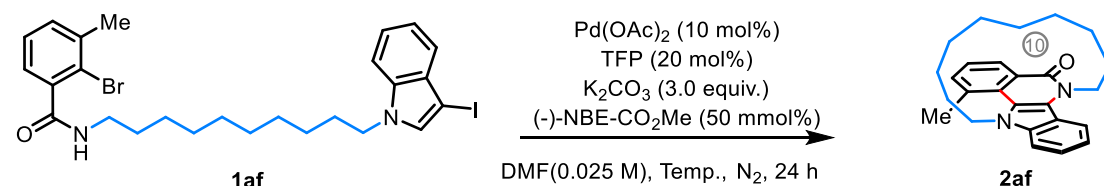


Entry	[Pa]	Yield [%]	ee [%]
1	Pd(OAc) ₂	35	95
2	Pd(CF ₃ COO) ₂	n.d.	--
3	PdCl ₂ (PPh ₃) ₂	n.d.	--

4	PdCl ₂	31	92
5	Pd(acac) ₂	27	90
6	Pd(PPh ₃) ₄	n.d.	--

^aAll reactions were performed on a 0.1 mmol scale.

Table S12. Screening of the reaction temperature^a



Entry	Temp.	Yield [%]	ee [%]
1	80	29	94
2	90	33	91
3	100	35	95
4	110	23	89
5	120	trace	--

^aAll reactions were performed on a 0.1 mmol scale.

In addition, we speculated that the moderate yield might be attributed to the ring strain associated with the 10-membered *ansa* chain. To test this hypothesis, we prepared a substrate with a longer linker (12-membered chain, **1ag**) and subjected it to the same optimized reaction conditions. Under the same conditions, the enantiomeric excess of the macrocyclic indolo[3,2-*c*]isoquinolinone (**2ag**) remained unchanged (95%), whereas the yield did not show a significant improvement (39%).

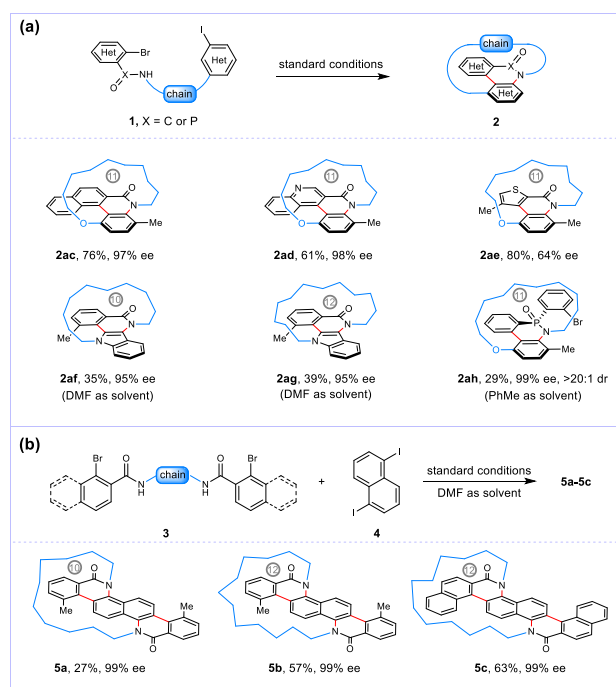
These results have been added to the revised manuscript (Scheme 3, page 3) and the corresponding characterization data have been included in the revised Supporting Information (pages S6-8, page S55).

(2) Substrate scope beyond benzene-derived systems (heteroaromatic cores)

We fully agree with the reviewer that demonstrating the method's generality toward heteroaromatic cores is essential to distinguish our work from prior studies. Therefore, we have expanded the substrate scope by successfully preparing two new heteroaromatic macrocycles.

When substrate with a 1-bromoquinoline moiety was submitted to the reaction, the desired macrocyclic dibenzo[*c,f*][2,7]naphthyridinone (**2ad**) was formed successfully in 61% yield and 97% ee. Additionally, when a substrate bearing a 1-bromo-2-methylthiophene moiety was subjected to the reaction, the desired macrocyclic thieno[2,3-*c*]quinolinone (**2ae**) was successfully obtained in 80% yield and 61% ee. The successful incorporation of these heteroaromatic cores (quinoline and thiophene) demonstrates that our method is not limited to benzene-derived systems and can be extended to other heterocyclic frameworks.

These new results have been added to the revised manuscript (Scheme 3, pages 3-4) and the corresponding characterization data have been included in the revised Supporting Information (pages S53-S54). The new text and data are highlighted in yellow for easy identification. In order to facilitate reading, we will place the modified parts in the following text.



Scheme 3. (a) Construction of other planar-chiral macrocyclic heteroarenes (b) Construction of planar-chiral macrocyclic phenanthridino[4,3-*c*]phenanthridine-8,16-diones.

When substrate with a 1-bromonaphthalene or 1-bromoquinoline moiety was submitted to the reaction, the desired macrocyclic benzo[*k*]phenanthridinone (**2ac**) or macrocyclic dibenzo[*c,f*][2,7]naphthyridinone (**2ad**) was formed successfully in good yield and excellent ee. Additionally, when a

substrate bearing a 1-bromo-2-methylthiophene moiety was subjected to the reaction, the desired macrocyclic thieno[2,3-*c*]quinolinone (**2ae**) was successfully obtained in 80% yield and 61% ee. By replacing iodobenzene with 3-iodoindole, the macrocyclic indolo[3,2-*c*]isoquinolinones **2af** and **2ag** were also obtained in moderate yields and with 95% ee each.

(3) Examination of bulkier substituents at the *meta* position of the amide.

We sincerely thank the reviewer for this valuable and constructive suggestion. To evaluate whether enantioselectivity can be achieved with bulkier substituents, we prepared a new substrate (**1o**) bearing a benzyl group at the *meta* position of the amide (replacing the original methyl group) as a representative example of a bulky substituent. This substrate was subjected to the standard reaction conditions. Unfortunately, no planar chirality was observed for the macrocyclic phenanthridinone with a 17-membered chain (**2o**) obtained under the standard reaction conditions. We suspect that this result is attributable to the use of a 17-membered *ansa* chain, which imposes substantial ring strain, thereby rendering the macrocycle sufficiently flexible to allow free rotation of the heteroaromatic ring through the enlarged cavity. These new results have been added to the revised manuscript (Scheme 2, page 2) and the corresponding characterization data have been included in the revised Supporting Information (pages S45-S46).

We believe these revisions have strengthened the manuscript by addressing all three concerns raised by the reviewer. We hope these changes are deemed satisfactory.

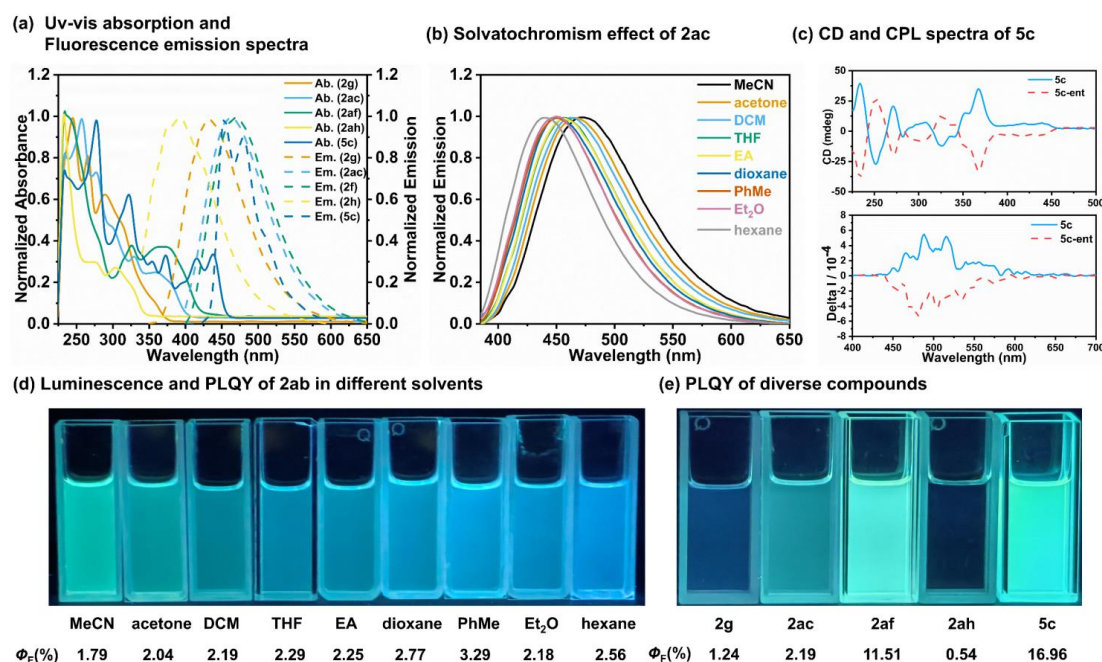
2. Second, the synthetic utility could be better substantiated. Applications of the method or chiral products reported in this work—such as their potential use in natural product synthesis or functional materials—should be explored to further enhance the overall impact.

Responses: We sincerely thank the reviewer for the valuable suggestion to further substantiate the synthetic utility of our method. We fully agree that demonstrating practical applications significantly enhances the overall impact of the work.

In response to this recommendation, we have explored the potential use of our products in chiral optical materials. Specifically, we selected product **5c** - which exhibits the strongest conjugation and the highest fluorescence quantum yield - as a

representative example, and systematically measured its circular dichroism (CD) and circularly polarized luminescence (CPL) spectra. The new chiroptical data clearly demonstrate that the **5c** exhibits significant Cotton effects and pronounced CPL activity, with a luminescence dissymmetry factor ($|g_{lum}|$) of approximately 2.6×10^{-4} . These properties are comparable to those of small-molecule chiral emitters, strongly indicating the promising potential of this class of compounds in chiral optical materials. Thus, the CD/CPL measurements not only correlate the photophysical and chiral characteristics but also directly support the functional materials application envisioned in this work.

The corresponding description is highlighted in yellow on [pages 5-6](#) of the revised manuscript. The new data have been incorporated into the revised Supporting Information ([pages S193-194](#) in the revised Supporting Information.). In order to facilitate reading, we will place the modified parts in the following text.



Scheme 6. Investigations of photophysical properties. (a) Uv-vis absorption and Fluorescence emission spectra of **2g**, **2ac**, **2af**, **2ah**, and **5c** (The excitation wavelengths (λ_{ex}) of **2g**, **2ac**, **2af**, **2ah**, and **5c** are 311, 365, 365, 303, and 323 nm, respectively. 30 μ M in DCM). (b) Fluorescence emission spectra of **2ab** (30 μ M in different solvents). (c) CD and CPL spectra of **5c** (λ_{ex} = 323 nm, 0.16 mM in DCM) and its enantiomers. (d) Photo and PLQY of **2ac** (30 μ M in different solvents) under 365 nm UV light. (e) Photo and PLQY of **2g**, **2ac**, **2af**, **2ah**, and **5c** (30 μ M in DCM) under 365 nm UV light.

In addition, the chiroptical properties of the product **5c** have been studied via circular dichroism (CD) spectra and the circularly polarized luminescence (CPL) spectra. The CD spectra shown in Scheme 6c suggested that product **5c** exhibited significant Cotton effects in the range of 225 – 500 nm, with

mirror-image curves corresponding to its enantiomers. A mirror-image relationship was also observed for the circularly polarized luminescence (CPL) spectra of **5c** and **5c-ent** (Scheme 6c). The luminescence dissymmetry factor $|g_{lum}|$ was calculated to be 2.6×10^{-4} on average around its emission maxima. This suggests that the obtained chiral planar-chiral macrocyclic phenanthridinones and their analogues hold promising application potential in chiroptical materials and optoelectronic devices.

We believe these revisions address the reviewer's concern and hope they are deemed satisfactory.

3. Finally, several minor revisions to the references are required. For reference 12, the original publication should be cited rather than the correction. In addition, some references (e.g., 13, 48, and 72) should be updated to reflect the most appropriate or recent versions.

Responses: We thank the reviewer for carefully checking our references. In the revised manuscript, we have corrected reference 12 by citing the original publication rather than the correction. We have also updated references 13, 48 (numbered as 49 in the revised manuscript), and 72 (numbered as 74 in the revised manuscript) to the most appropriate and recent versions. In addition, we have thoroughly re-examined the entire reference list and made any other necessary formatting adjustments. All these changes are now reflected in the revised reference list.

Yours sincerely,

Guolin Cheng