nature portfolio

Peer Review File

Asymmetric Büchner reaction and arene cyclopropanation via copper-catalyzed controllable cyclization of diynes

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

The manuscript by Ye, Hong and co-authors presents an intriguing Cu-catalyzed enantioselective Büchner reaction and arene cyclopropanation. By this method, a diverse array of chiral tricycle-fused cycloheptatrienes and benzonorcaradienes skeletons can be achieved with high yields and with excellent enantioselectivities. The reaction proceeds via a diyne cyclization to generate the vinyl cation intermediate, followed by nucleophilic attack process to yield the desired dearomatized products. DFT calculations further validate the vinyl cation-involved mechanism of arene cyclopropanation and Büchner reaction. This approach enables the diversification of asymmetric arene Büchner and cyclopropanation reactions, making this contribution particularly noteworthy, in terms of the limited exploration of asymmetric arene cyclopropanation reactions based on alkynes. Consequently, I recommend publishing this nice work in Nature Communications after revisions as follows:

1. To enhance the readability and context for readers, I suggest citing recent exemplary studies on the chiral rhodium-catalyzed enynone cycloisomerization, for instance, the article in Chem. Soc. Rev., 2020, 49, 908.

2. I wonder if the Ar group in substrate 1 can be substituted with the alkyl group.

3. In the section discussing the scope of cyclopropanation (Fig. 4), I notice a potential discrepancy in the title. Kindly verify its accuracy.

4. In the proposed reaction mechanism (Fig. 6), the structure of TSB1 is suggested to be in accordance with the structure of TSB2.

Reviewer #2 (Remarks to the Author):

Ye, Hong, and coworkers report a copper catalyzed cyclization of biaryl ynamideynes that results in the formation of either the pentacyclic pyrrole product by (formal) cyclopropanation or a corresponding tetracyclic cycloheptatriene substituted pyrrole by (formal) Buechner reaction. Products were obtained in uniformly excellent yield (80-99%) and enantioselectivity (>90% in almost all cases) for a combined total of 54 examples. The reactions can be carried out on gram scale, and the densely functionalized products are amenable to a variety of further derivatizations.

While the examples are numerous, the intricately designed substrates used in this transformation makes a product with relatively modest synthetic utility. Meanwhile, this is considerable similarity in substrate design with respect to the Wu group's 2019 JACS article (10.1021/jacs.9b09303).

On the other hand, there is some claim to mechanistic novelty. The proposed mechanism for the transformation involves the formation of a heterocycle- and metal-stabilized vinyl cation that undergoes a stepwise cyclopropanation with the pendent aryl ring. However, the authors give scant evidence for this proposal. The alternative pathway, in which a copper carbene directly undergoes cyclopropanation is possible. This pathway would make the mechanism identical to the one proposed in the JACS paper, save for switching out an alkene and replacing it with an arene.

In order for this paper to be suitable for Nat. Commun. on novelty grounds, the authors need to show that the mechanism of this transformation is indeed dichotomous to their previous report. The justification for this claim is a statement that the copper would coordinate to the more electron-rich alkyne. This is dubious as R2 and R3 are both also very electron-rich. In any case, more favorable reversible binding does not imply that the subsequent addition of the pi nucleophile must take place there! While a stereochemical model supports the possibility of this mechanism, that in itself is not sufficient to rule out the other possibility.

1) Computations for the alternative pathway (analogous to the 2019 JACS paper) should be done. Conversely, perhaps the current mechanism is the correct one for this previously reported alkene cyclopropanation reaction? If they indeed proceed through distinct

mechanisms based on where the copper coordinates, the different between these systems needs to be clarified.

2) Is it possible to obtain experimental evidence for this mechanism? For instance, a Hammett study may be able to distinguish between these pathways. A trapping study may also reveal a mechanistic distinction.

3) It looks like the aryl tether can be replaced by a cyclic alkene in 2ab and 4z. Do other ring sizes or an acyclic tether work? Can it be a simple alkyl group, a cyclopropyl, or heteroatomic?

Either making a convincing case that the mechanism is different than before (points 1 and/or 2) or showing broader scope that would suggest more general synthetic utility (point 3) should be addressed before this manuscript is suitable for further consideration by Nat. Commun.

Signed: Yiming Wang

Reviewer #3 (Remarks to the Author):

Ye et al. reported an asymmetric büchner reaction and arene cyclopropanation via copper-catalyzed controllable cyclization of diynes. The protocol works by controlling the diynyl substrate to access the chiral tricycle-fused cycloheptatrienes and benzonorcaradienes in high yields and enantioselectivities. Methodologically, it is a valuable reaction. I am interested in these two competitive reactions and enantioselective mechanisms. However, before being considered for acceptance by Nat. Commun., the following points need to be addressed regarding theoretical mechanisms.

(1) 1,4-H-migration is considered by the authors as the enantioselectivity determining step. The energy barrier difference between TSE1(R) and TSE1(S) is just 1.4 kcal/mol (23.0 vs 24.3). This energy barrier difference is even within the DFT theory calculation error.

Although 1,4-H-migration is the rate determining step for the conversion, the cyclopropanation is the first step in the construction of chirality, and therefore the cyclopropanation step cannot be ignored when discussing chirality.

(2) In Fig. 6(b), the total energy barrier of 26.4 kcal/mol seems to be too high relative to this bimolecular reaction at 0°C. Have the authors tested other theoretical methods in including, but not limited to, this step?

(3) At the 1,4-H-migration step, has the mechanism been calculated without H2O assistance? In addition, the source of H2O in the two current reaction systems also needs to be shown.

Reviewer #4 (Remarks to the Author):

This article deals with the Cu-complex-catalyzed cycloisomerization of diynes that is leading to the formation of chiral cycloheptatrienes (28 examples) or norcaradienes (26 examples) in excellent yields and excellent enantioselectivities via a Büchner reaction or a cycloprapanation respectively. The reaction proceeded using 10 mol% of a cationic Cu(I) catalyst in toluene at -20°C for 40 h in the case of the Büchner reaction and in 2-methyltetrahydrofurane at 0°C for 40 h in the case of the cyclopropanation reaction.

The article is well written and correctly presented. The structure of molecule 5g in Fig. 5 should be corrected to appear more clearly.

The Supporting information is correctly presented and the products are well caracterized. The text below the Fig S5 is unclear : the authors state a conversion of 51% for the conversion of 2i' into 2i that do not correspond to the data presented on the figure.

Regarding the mechanistic rationale, the authors propose a H2O-assisted 1,4-H migration as the enantiodetermining step but never give accurate data regarding the influence of the quantity of water on the enantioselectivity. This point should be clarified to allow a good reproducibility of the results. It would be nice to know what happens if water is rigorously excluded. Would it have an effect on the reaction rate or the product distribution ? What would happen if other H-donors, including chiral ones, were added to the reaction mixture ?

Regarding the cyclopropanation part, although the product described are highly interesting from the mechanistic point of view, the substrate scope is extremely limited to 2-naphthalenyl-substituted diynes. This point should be discussed in the manuscript and highlighted in more details (including for example data from the Fig S3 and S4 or any other unpublished data that would give information about the chemoselectivity of the two competitive catalyzed reactions).

In conclusion, this manuscript meets the criteria of novelty and significance of Nature Communications and could be published after the comments listed above were taken into account.

Reviewer #5 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

XIAMEN UNIVERSITY
Xiamen, Fujian, China

August 16, 2024

Here are my responses to those comments by the reviewers **point-by-point** and the changes made to the manuscript (revised portions are marked with a yellow background in the paper).

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):
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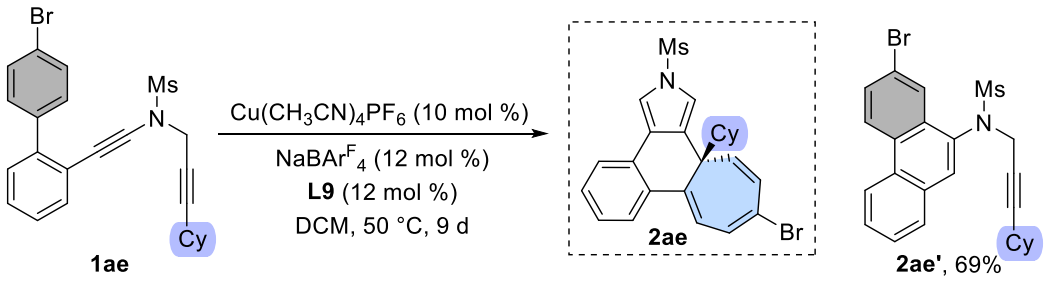
1. Response to comment (reviewer 1):
1) To enhance the readability and context for readers, I suggest citing recent exemplary studies on the chiral rhodium-catalyzed enynone cycloisomerization, for instance, the article in Chem. Soc. Rev., 2020, 49, 908.

- We first thank the reviewer very much for the kind recommendation and careful evaluation.
- As suggested, we have added this review paper as reference 36.

2. Response to comment (reviewer 1):
2) I wonder if the Ar group in substrate **1** can be substituted with the alkyl group.

- Based on the reviewer's comments, we attempted to replace the aromatic ring with the Cy group, but found that the reaction failed to obtain the corresponding Büchner product using this substrate, and instead a hydroarylation product was obtained in 69% yield. We have included the experimental results in the Supplementary Information (Fig. S1).



3. Response to comment (reviewer 1):

3) In the section discussing the scope of cyclopropanation (Fig. 4), I notice a potential discrepancy in the title. Kindly verify its accuracy.

- As suggested, we have revised the title of Fig. 4 to "Scope of Asymmetric Cyclopropanation of *N*-Propargyl Ynamides **3**".

4. Response to comment (reviewer 1):

4) In the proposed reaction mechanism (Fig. 6), the structure of **TSB1** is suggested to be in accordance with the structure of **TSB2**.

- As suggested, we have modified **TSB2** accordingly.

Reviewer #2 (Remarks to the Author):

Ye, Hong, and coworkers report a copper catalyzed cyclization of biaryl ynamideynes that results in the formation of either the pentacyclic pyrrole product by (formal) cyclopropanation or a corresponding tetracyclic cycloheptatriene substituted pyrrole by (formal) Buechner reaction. Products were obtained in uniformly excellent yield (80-99%) and enantioselectivity (>90% in almost all cases) for a combined total of 54 examples. The reactions can be carried out on gram scale, and the densely functionalized products are amenable to a variety of further derivatizations.

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5. Response to comment (reviewer 2):

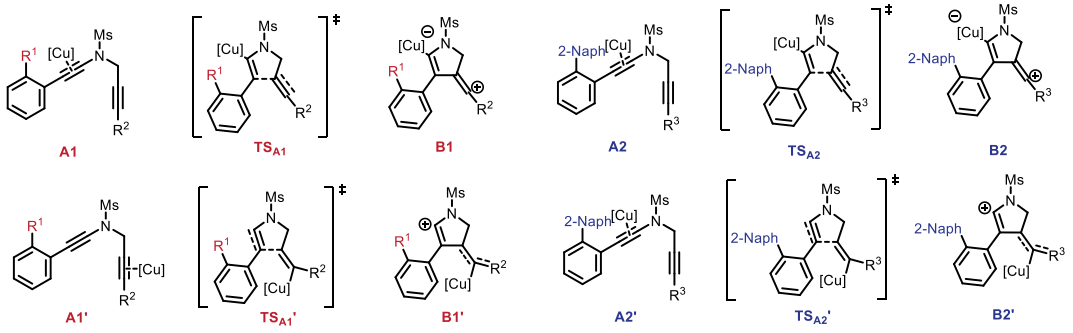
5) Computations for the alternative pathway (analogous to the 2019 JACS paper) should be done. Conversely, perhaps the current mechanism is the correct one for this previously reported alkene cyclopropanation reaction? If they indeed proceed through distinct mechanisms based on where the copper coordinates, the different between these systems needs to be clarified.

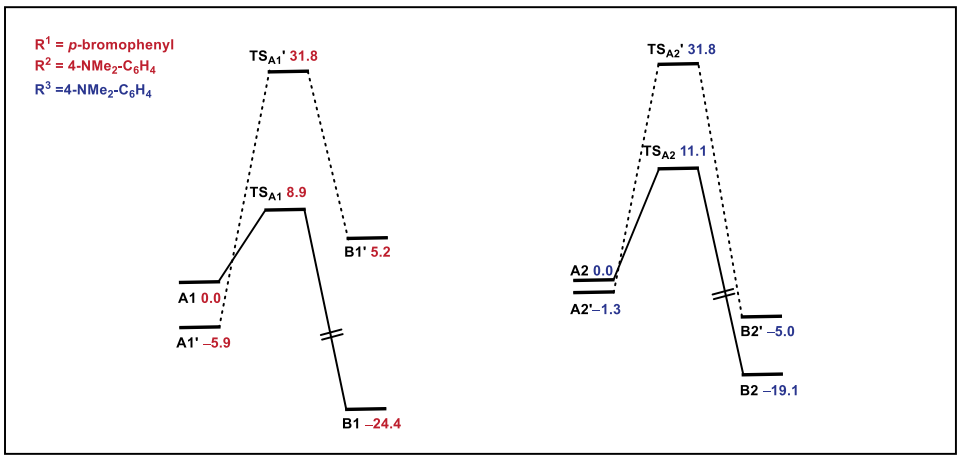
- We acknowledge the valuable suggestions from reviewer 2.
- In both systems, we computed the free energy barriers for the nucleophilic cyclization step of the alternative pathway (analogous to the 2019 JACS paper) and compared with that of the pathway presented in this manuscript. The results of DFT computations indicate that the free energy barrier of the alternative pathway is 31.8 kcal/mol, which is hard to proceed under the given experimental conditions. Therefore, the pathway in this manuscript in which the copper species coordinates the electron richer -C≡C- bond is much more dynamically preferred in the next reaction steps.

ΔG_{298K}

(PCM, solvent = toluene)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ

(PCM, solvent = 2-MeTHF)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ





- Importantly, further detailed DFT computations revealed that the substrates (**1a** and **3x**) as Lewis base actually assisted the 1,4-H migration step in the current system, and the enantioselectivity-determining factor was then systematically studied according to the new free energy diagram. Please see entry 8 (Response to reviewer 3) for details.

6. Response to comment (reviewer 2):

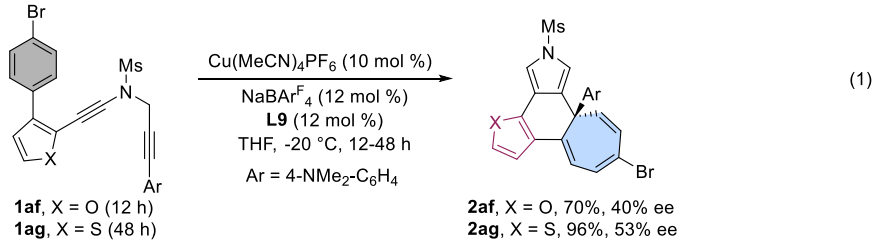
6) Is it possible to obtain experimental evidence for this mechanism? For instance, a Hammett study may be able to distinguish between these pathways. A trapping study may also reveal a mechanistic distinction.

- Thank you very much for the valuable suggestion. We do recognize the importance of conducting more experiments to validate our proposed mechanism, including Hammett experiments. However, when the propargyl amide moiety of diyne is directly connected with the electron-deficient aromatic rings, the experimental results are not satisfactory, requiring high temperatures and with low ee values (<10% ee, see Fig. S3 for details), which prevents us from collecting sufficient data to establish an accurate Hammett equation.

7. Response to comment (reviewer 2):

7) It looks like the aryl tether can be replaced by a cyclic alkene in **2ab** and **4z**. Do other ring sizes or an acyclic tether work? Can it be a simple alkyl group, a cyclopropyl, or heteroatomic?

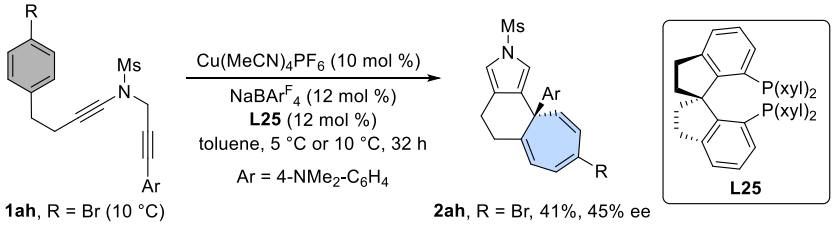
- We acknowledge the valuable suggestions from reviewer 2.
- As suggested, we synthesized these diyne substrates. As shown in eq 1, the asymmetric Büchner reaction could proceed efficiently with the heterocycle-linked diynes **1af**–**1ag** to deliver the corresponding cycloheptatriene products **2af**–**2ag** in 70–96% yields under the optimized reaction conditions, but only gave moderate enantioselectivities (40–53% ees). The asymmetric Büchner reaction also occurred smoothly with the alkyl-linked aryl diynes **1ah**–**1ai** under the optimized reaction conditions, but only gave moderate yields (41–42% yields) and enantioselectivities (45–52% ees, eq 2). Interestingly, the asymmetric arene cyclopropanation proceeded well with the heterocycle-linked diynes **3ac** and **3ad**, furnishing the corresponding cyclopropanes **4ac** (99%, 74% ee) and **4ad** (96%, 93% ee), respectively (eqs 3-4). In addition, the arene cyclopropanation of the alkyl-linked naphthyl-diyne **3ae** was also investigated, affording the desired benzonorcaradiene **4ae** in 90% yield with 42% ee under the optimized reaction conditions (eq 5). Finally, it was found that the use of the cyclopropyl-linked aryl diyne **1aj** only led to the formation of the corresponding cyclopropane prodcut **4aj** in 38% yield with 20% ee (eq 6). Attempts to synthesize other aryl-substituted cyclopropyl-linked diynes failed. Thus, we believe that the aryl linker here played an important role in promoting the reactivity and enantioselectivity, which was actually also observed in our previous diyne chemistry (ref. 46-53). We have included these experimental results in the manuscript and Supplementary Information.



1af, X = O (12 h)
1ag, X = S (48 h)

2af, X = O, 70%, 40% ee
2ag, X = S, 96%, 53% ee

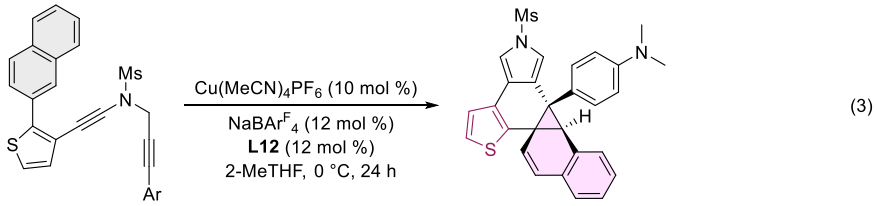
(1)



1ah, R = Br (10 °C)
1ai, R = F (5 °C)

2ah, R = Br, 41%, 45% ee
2ai, R = F, 42%, 52% ee

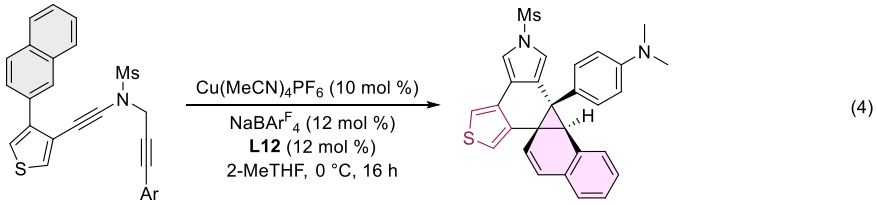
(2)



3ac

4ac, 99%, 74% ee

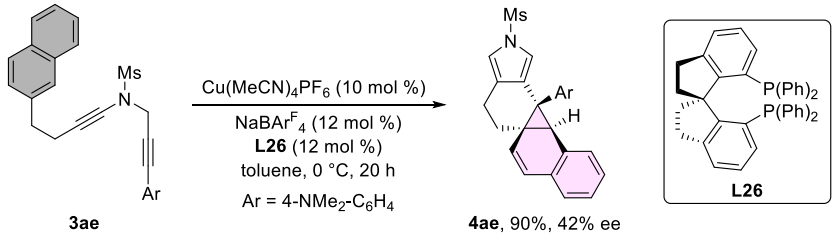
(3)



3ad

4ad, 96%, 93% ee

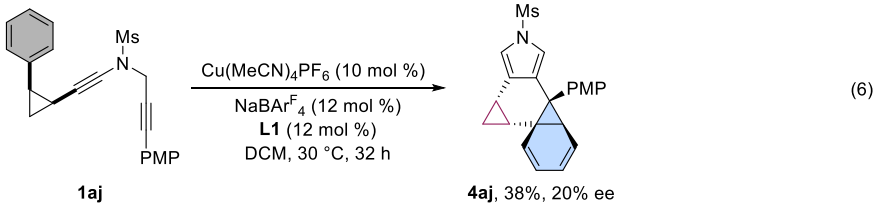
(4)



3ae

4ae, 90%, 42% ee

(5)



1aj

4aj, 38%, 20% ee

(6)

Either making a convincing case that the mechanism is different than before (points 1 and/or 2) or showing broader scope that would suggest more general synthetic utility (point 3) should be addressed before this manuscript is suitable for further consideration by Nat. Commun.

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8. Response to comment (reviewer 3):

8) 1,4-H-migration is considered by the authors as the enantioselectivity determining step. The energy barrier difference between TSE1(R) and TSE1(S) is just 1.4 kcal/mol (23.0 vs 24.3). This energy barrier difference is even within the DFT theory calculation error. Although 1,4-H-migration is the rate determining step for the conversion, the cyclopropanation is the first step in the construction of chirality, and therefore the cyclopropanation step cannot be ignored when discussing chirality.

9) In Fig. 6(b), the total energy barrier of 26.4 kcal/mol seems to be too high relative to this bimolecular reaction at 0 °C. Have the authors tested other theoretical methods in including, but not limited to, this step?

10) At the 1,4-H-migration step, has the mechanism been calculated without H_2O assistance? In addition, the source of H_2O in the two current reaction systems also needs to be shown.

- We acknowledge the valuable suggestions from the reviewer which helped us a lot in promoting the quality of our manuscript. Actually, we performed detailed computational studies on the 1,4-H migration step in our previous work (*Chem. Sci.* **2021**, *12*, 9466; DOI: 10.1039/D1SC02773J), which encompasses investigations into various 1,4-H migration mechanisms, including bimolecular hydrogen exchange, protecting group-assisted 1,4-H migration, water-assisted, and base-assisted 1,4-H migration (as detailed in Supplementary Figure 8). Our calculations indicate that water-assisted and base-assisted pathways exhibit lower energy barriers, providing crucial insights into the reaction mechanism. In our research work of this manuscript, to clarify the role of water molecule in enantioselectivity-determining, we conducted further experimental investigations and discovered that the enantioselectivity had hardly changed in the absence of water. Please see entry 11 (Response to reviewer 4) for details. Therefore, we deduced that the 1,4-H migration step should be assisted by other Lewis base in the current system and is not the enantioselectivity-determining step.
- We conducted further DFT computations on the Lewis base-assisted 1,4-H migration step and discovered that the substrates (**1a** and **3x**) could indeed assist the 1,4-H migration step as Lewis base, and the free energy barrier of which was 13.8 kcal/mol

and 20.1 kcal/mol, respectively. Thus, both could occur smoothly under the given experimental conditions.

- We also conducted further DFT computations on [Cu**L9**]-**TS$_{B1}$** and [Cu**L12**]-**TS$_{B2}$** including the nucleophilic attack of electron-rich aryl groups to the vinyl cation, which is thought to be enantioselectivity-determining according to the new free energy diagram. The free energy differences between [Cu**L9**]-(*S*)-**TS$_{B1}$**&[Cu**L9**]-(*R*)-**TS$_{B1}$** and [Cu**L12**]-(*S*)-**TS$_{B2}$**&[Cu**L12**]-(*R*)-**TS$_{B2}$** are 4.8 kcal/mol and 4.0 kcal/mol, respectively, which well support the experimentally obtained *ee* values.
- For further studies on the influence of water, please see entry 11 (Response to reviewer 4) for details.

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9. Response to comment (reviewer 4):
11) The article is well written and correctly presented. The structure of molecule **5g** in Fig. 5 should be corrected to appear more clearly.

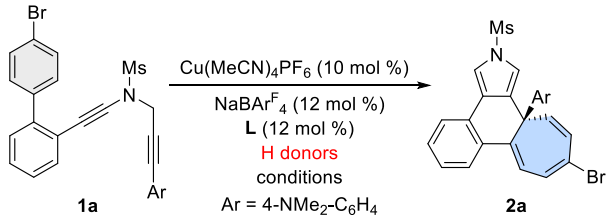
- We thank the reviewer very much for the kind recommendation and pertinent comments.
- Based on the suggestions, we have redrawn molecule **5g** to make it clearer.

10. Response to comment (reviewer 4):
12) The Supporting information is correctly presented and the products are well caracterized. The text below the Fig S5 is unclear : the authors state a conversion of 51% for the conversion of **2i'** into **2i** that do not correspond to the data presented on the figure.

- Very sorry for this mistake. We have revised the conversion of **2i'** into **2i** to be consistent with the figure, which is 41%.

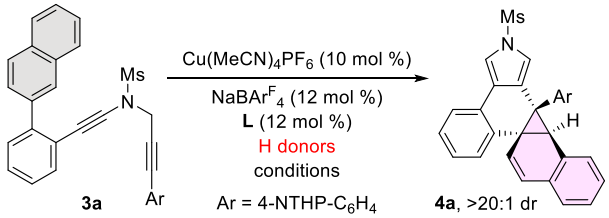
11. Response to comment (reviewer 4):
13) Regarding the mechanistic rationale, the authors propose a H_2O-assisted 1,4-H migration as the enantiodetermining step but never give accurate data regarding the influence of the quantity of water on the enantioselectivity. This point should be clarified to allow a good reproducibility of the results. It would be nice to know what happens if water is rigorously excluded. Would it have an effect on the reaction rate or the product distribution ? What would happen if other H-donors, including chiral ones, were added to the reaction mixture ?

- As suggested, we performed these control reactions and found that the equivalent of water had little impact on the enantioselectivity but led to light differences in reactivity and yield, which is in accordance with our previous work (*Chem. Sci.* **2021**, *12*, 9466; DOI: 10.1039/D1SC02773J). In the absence of water, these reactions gave similar enantioselectivities. Please see the following two Tables for details.
- The use of other H-donors such as DTBMP also gave similar enantioselectivities.
- Importantly, detailed theoretical calculations revealed that bimolecular-assisted process was more likely involved in the 1,4-H migration. Please see entry 8 (Response to reviewer 3) for details.



entry	H donors	time	yield(%)[b]	ee (%)[c]
1	H_2O (0 equiv)	137 h	94	96
2	H_2O (0.5 equiv)	119 h	90	95
3	H_2O (1 equiv)	119 h	84	95
4	H_2O (3 equiv)	119 h	87	96
5	H_2O (5 equiv)	125 h	94	95
6	DTBMP (1 equiv)	125 h	73	95

[a]Reaction conditions: **1a** (0.05 mmol), $Cu(MeCN)_4PF_6$ (0.005 mmol), **L9** (0.006 mmol), $NaBAr^F_4$ (0.006 mmol), toluene (dry, 1 mL), -20 °C, in vials. [b]Measured by ^1H NMR using diethyl phthalate as internal standard. [c]Determined by HPLC analysis. DTBMP = 2,6-Di-*tert*-butyl-4-methylpyridine.



entry	H donors	time	yield(%)[b]	ee (%)[c]
1	H_2O (0 equiv)	89 h	90	96
2	H_2O (0.5 equiv)	89 h	95	96
3	H_2O (1 equiv)	118 h	93	96
4	H_2O (3 equiv)	131 h	99	96
5	H_2O (5 equiv)	144 h	90	96
6	DTBMP (1 equiv)	89 h	78	96

[a]Reaction conditions: **3a** (0.05 mmol), $Cu(MeCN)_4PF_6$ (0.005 mmol), **L12** (0.006 mmol), $NaBAr^F_4$ (0.006 mmol), 2-MeTHF (dry, 1 mL), 0 °C, in vails. [b]Measured by ^1H NMR using diethyl phthalate as internal standard. [c]Determined by HPLC analysis. DTBMP = 2,6-Di-*tert*-butyl-4-methylpyridine.

12. Response to comment (reviewer 4):

14) Regarding the cyclopropanation part, although the product described are highly interesting from the mechanistic point of view, the substrate scope is extremely limited to 2-naphthalenyl-substituted diynes. This point should be discussed in the manuscript and highlighted in more details (including for example data from the Fig S3 and S4 or any other unpublished data that would give information about the chemoselectivity of the two competitive catalyzed reactions).

- As noted by the reviewers, the asymmetric reaction on the cyclopropanation part was indeed limited to the 2-naphthyl-substituted diynes. The use of 1-naphthyl diyne substrate could lead to the corresponding cyclopropane product in good yield but with only moderate enantioselectivity after a series of condition optimization experiments. We hypothesize that the moderate enantiomeric excess (ee) values may be attributed to the steric hindrance between the bridging benzene ring and the dearomatized naphthalene ring in the obtained product, as illustrated in the figure below. As suggested, these results have been put in the manuscript and discussed in details.

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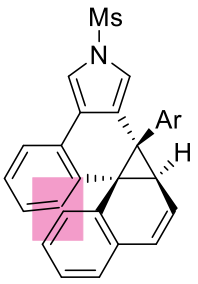

Reviewer #5 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

This is an excellent contribution to both alkyne chemistry and carbene chemistry. The authors have addressed all of my concerns. Congratulations to the authors.

It could be accepted in its current form.

Reviewer #2 (Remarks to the Author):

The authors have provided a revised manuscript that addresses my concerns about the mechanism and provides more insight into the scope of the reaction, including the results on more "stripped down" substrates which give the expected products, though with lower selectivities. Addressing my previous concerns, the mechanism is shown to proceed preferentially via an acyclic vinyl cation, rather than an alpha-N cation proposed in the authors' earlier work. In addition, further DFT studies have provided additional information regarding the means of enantioinduction and the final 1,4-H transfer step. Overall, this manuscript serves as a thorough and interesting study that will serve to inspire further development of enantioselective Cu-catalyzed processes, and I recommend acceptance for publication.

Yiming Wang

Reviewer #3 (Remarks to the Author):

The author has responded well to our concerns. For the theoretical calculation that I pay more attention to, the authors have also performed the necessary additional calculations. The calculation results are reasonable. Therefore, I agree to publish this manuscript.

Reviewer #4 (Remarks to the Author):

The modifications made to the documents answer the points raised during the review process. More specifically, the new reaction pathway presented on Fig. 6 excluding a H2O-assisted 1,4 H-migration is more convincing than the previous one and correlates with the experimental observation of an absence of influence of added water on the enantioselectivity of the transformation.

As such, the manuscript is suitable for publication.

Reviewer #5 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.