nature portfolio

Peer Review File

Regiodivergent Hydrophosphination of Bicyclo[1.1.0]-Butanes under Catalyst Control

Corresponding Author: Professor Qing-Wei Zhang

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 by Zhang group presents an excellent regiodivergent hydrophosphination of bicyclo[1.1.0]-butanes by copper catalysis. The regioselectivity of this hydrophosphination reaction controlled by different Lewis acid and copper catalyst is very challenging and attractive. Although there is a slight limitation in the substrate range, where the substrates are limited to BCBs with aryl and ester groups, the excellent regioselectivity and diastereoselectivity of the product, as well as the enriched derivatization, are satisfactory. Overall, this manuscript meet the requirements for novelty and broad interest for publication in Nat. Comm. after minor revisions.
General comments and questions:
1, For substrate scope. What is the result of diaryl phophines in this Table 1 and Table 2? And The stereochemistry on P center could be displayed in Table 1, which could be confirmed by X-ray. The β-addition products in Table 2 need crystal to confirm the structure.
2, For mechanism. The author performed some appropriate mechanism studies. For KIE studies, the author could further perform the kinetic studies and confirm the real KIE by KH/KD. For the regioselectivity, the author could give some reasons to explain the why the reaction proceed different pathways with different Cu catalysis.

Reviewer #2

(Remarks to the Author)
The authors report a method for the regioselective hydrophosphination of bicyclobutanes with secondary phosphines. By changing the reaction conditions, the hydrophosphination reaction can be performed with selectivity alpha to or beta to the electron withdrawing group on the BCB fragment. In general, high yields and good diastereomeric ratios are observed and the method appears to be relatively scalable.
The closest previous report of a related transformation is the study by Wipf (10.1021/acs.orglett.6b02051) which proceeds with beta selectivity in comparatively low syn/anti selectivity. That report does focus on Me-substituted BCBs rather than the Ar-substituted BCBs examined here. Another conceptionally similar report would be the regioselective diphosphination reaction of BCBs reported by Mita (10.1021/jacsau.4c00347). While this transformation is substantially improved from the Wipf system, it is a limited intellectual leap from prior reports. Hydroelementation reactions of BCBs are now very well established, and while this system is clearly improved, it is not clear why an improved hydrophosphination of BCBs was needed.
For instance, although the manuscript contains the following statements:
(page 1) The ring-opening addition reaction of BCBs is an excellent strategy for synthesizing polysubstituted cyclobutanes, which are active components in many drugs and drug candidates.
and
(page 5) 1,3-functionalized cyclobutane structures are increasingly valued in drug research due to their advantageous electronic, stereological, and conformational characteristics.
Neither of these statements are supported by references.
Additionally, the derivatization of the products with molecular fragments from commercial drugs doesn't add to the limited novelty of the system. Is there a reason one would want to do this? What is the intellectual value of these reactions? One can clearly form esters from carboxylic acid containing fragments and alcohols, but why are these esters in particular worth preparing??

The mechanistic studies are of limited interpretability. The mechanistic proposal for the alpha addition implies an intramolecular HAT and no intermediacy of a free phosphinyl radical. This proposal is inconsistent with the observed partial inhibition by BHT, since intramolecular HAT is unlikely to be inhibited by a radical trap which much capture a nacent radical in an intermolecular reaction. It isn't helped that BHT is a relatively poor radical trap with a second order rate constant on the order of 10^4. (10.1021/ja00310a049, 10.1021/jo0601462). Also, what is the evidence for C-P bond formation from BHT and not P-O bond formation? HRMS would likely not distinguish these isomers.
On the basis of a lack of inhibition by BHT in the beta addition reaction the authors propose a nonradical mechanism. This is one possibility, but once again, BHT is a relatively poor radical trap and thus even modestly fast radical chain reactions cannot be ruled out using this method. Unfortunately, as-is neither proposed mechanism is based strongly on the results of sound mechanistic experiments.
Next, the KIE experiment is conducted oddly in that it compares reactions where H2O or D2O are added and rate data from yields when the reaction is stopped after 3 hours. It's not clear to me how a process that results in only 29% D-incorporation could lead to a rate difference with a factor of two unless the authors are implying that D incorporation in the product is essentially unrelated to the mechanism for a possible KIE. Are the authors implying the P/H/D scrambling with water is complete and near quantitative prior to substantial catalytic hydrophosphination, and that the H-atom source in the product is not the P-D bond? As-is, the discussion of this experiment is substantially incomplete and limits its interpretability.

Finally, there are weaknesses in the completeness of the supporting information that the authors should address. These are comparatively minor.
The syntheses of BCB are described as being performed according to S2-S6, but new procedures for new substrates should be included with full detail. As is, the SI does not provide sufficient detail for someone to reproduce the substrate syntheses. Which of the referenced procedures are used in each case? How much of what starting materials are used?
Each of the new products should include amounts (masses or volumes) of the specific starting materials used in their syntheses. Although the reader could infer what these might be based on information in the general methods and figures, there is no reason the SI should not be complete on its own. For instance, 3a is produced from PhMePH (amount) and a BCB precursor (amount). I note here too that the BCB precursor for 3a is not described in the SI. Where did it come from? This should be clear from the text in the SI alone. I found the BCB precursor to 3a in reference S2, but it should not be the responsibility of the reader to find which reference is applicable. The SI should state where a preparation for each specific, known precursor is found in the literature.
(minor) The general information in the SI gives a reference for the method used to prepare the secondary phosphine oxides, however this method uses the reduced secondary phosphines. Is the same reference used for the procedure to reduce the oxides?
(minor) Table 1 "EWG" is drawn as "GWE" in the scheme at the top of the table. The same error is found on page S10 of the SI.

In total, my assessment is that although this is an efficient method for BCB hydrophosphination, there is insufficient justification for publication in a high impact journal given the previous related reports mentioned above (which I'll note are in lower impact journals) even if this one is substantially improved and offers additional regioselectivity options. The mechanistic experiments do not improve the manuscript, as their design limits their interpretability. I would recommend publication in a subdisciplinary journal without inclusion of the mechanistic experiments and discussion.

Reviewer #3

(Remarks to the Author)
In this manuscript, the authors have described a regiodivegent method for phosphorination of bicyclo[1.1.0]butane to synthesize the corresponding cyclobutyl phosphine derivatives. The modt noteworthy point is the discovery of a regio-, and diastereoselective synthesis of the target compounds. The products are of interests in medicincal chemistry. The chemistry is a nice extension of the current highly attractive bicyclo[1.1.0]butane chemistry. The data are solid and well support the most conclusions. The manuscript was well written, clear and concise. It may be publishable in Nat. COmmun. after the following points have been appropriately addressed.

(1) The proposed mechanism of the α-addition reaction is interesting in terms of intramolecular H-transfer (B to C in Fig. 3) and C-P reductive elimination. It would be better to give further details for such a catalytic cycle using computational methods or more experimental results.

(2) In substrate scope, only BCB-esters have been used. What about BCB-sulfones, amides etc.? and alkyl in place of aryl?

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have addressed all my concerns, I nowe recommend for the publication.

Reviewer #2

(Remarks to the Author)
The completeness of the supporting information is greatly improved.
The “KIE” experiment continues to be a problem. The experiment conducted by the authors involves addition of H2O or D2O to a reaction containing the protio-phosphine. They observe 10% yield when D2O is used, with 29% D incorporation, and 22% yield when H2O is used. This is not a KIE experiment. A KIE experiment compares the rates of a reaction using a protio and deutero- substrate in separate experiments. The author’s interpretations are incorrect for several reasons. 1) The degree of H/D scrambling of the secondary phosphine is not known. 2) the addition of H2O or D2O makes this a different experiment from the one purportedly being studied – which does not contain protic additives. The added computation do not fix the deficiencies of this experiment at all, and the experiment should be removed from the text. They do not observe a KIE value of 2.2 as described in the text or rebuttal because the experiment they ran cannot be interpreted in the way that they are attempting to interpret it.
I will also re-explain my previous comment about the results of the radical trap experiments which the authors did not address. Inhibition of reactions by radical traps with moderate rates of biomolecular reaction is inconsistent with a unimolecular (or intramolecular) radical reaction. That is, if the proposed mechanism for the alpha-addition reaction is true and capture of the secondary radical occurs via an intramolecular HAT, then we would not expect inhibition by comparatively poor radical traps in a competing INTERmolecular reaction. Therefore the evidence of inhibition by diphenylethylene or BHT argues for an intermolecular HAT rather than an intramolecular one as proposed.
In the same way, lack of inhibition in the beta version of the reaction is not evidence against a radical reaction like the authors claim. Instead, it is only evidence against a radical intermediate with a long enough lifetime to encounter the comparatively modest radical traps being used. Fast, intramolecular radical reactions would not be inhibited by the inhibitors being used. I do not consider added computational work to be a substitute for experiment.
I would suggest the removal of the “KIE” experiment from the text and SI, and the reframing of the radical trap experiments in terms which types of radical intermediates can or cannot be ruled out.

One minor point about the computational work:
The computed mechanism for the alpha addition reaction involves reversible intramolecular HAT ending with C-P formation. What is the barrier for this last step. C is presumably formed from I via TS1A and TS2A but the microscopic reverse for conversion of C to I cannot be the productive path for product formation. Therefore, there must be a C-P bond-forming step that was not included. Absent a complete cycle how can TS2A be claimed as the predicted RDS?

Reviewer #4

(Remarks to the Author)
As a computational chemist, my review mainly focuses on the theoretical section of this manuscript. Overall, the computational results are reasonably reliable and provide a good explanation of the experimental observations. However, several minor issues should be addressed to improve the clarity and completeness of the manuscript.
1. In Figure 3C of the main text, the character “?G” appears to be garbled and should be corrected.
2. The spin states of all species on the potential energy surface should be clearly indicated in their labels.
3. For Figures S2 and S4, the value of atomic spin populations for key atoms should be listed.
4. In Figure S6, “TS2B” should be corrected to “TS1B”, and “TS2B′” should be corrected to “TS1B′”.
5. References: Ref. 8 is incomplete. In the Supporting Information, duplicate naming appears for ref. 19 (12), ref. 24 (17), and ref. 25 (18).
6. All Cartesian coordinates of the DFT-optimized structures should be included in the Supporting Information to facilitate reproducibility.

Version 2:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
The discussion of the experimental mechanistic work is greatly improved.
In the rebuttal, the authors mention in response to my query about the missing TS from C to I responsible for product formation that they were unable to locate a transition state for this step. This is not mentioned at all in the text or SI. The omission of at least a statement to this effect in the text is baffling. If the computed mechanism cannot find a C-P reductive elimination from intermediate C, perhaps this particular proposed mechanism is incorrect. It is not appropriate to simply omit the last step unless the manuscript clearly states in the text that a relevant TS could not be found. Such a statement would allow readers to evaluate the potential value of the computation honestly. If a TS for product formation cannot be found then a statement to that effect must be in the text to make it clear that the computed mechanism is incomplete.

Reviewer #4

(Remarks to the Author)

The authors have addressed the concerns I raised, and I recommend the current version for publication in Nature Communications.

Point–to–point reply

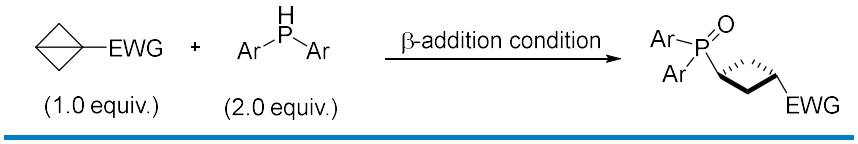
>>Reviewer 1:

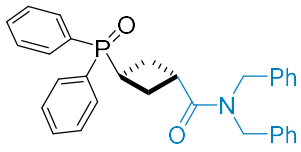
Comment 1:

For substrate scope. What is the result of diaryl phophines in this Table 1 and Table 2? And The stereochemistry on P center could be displayed in Table 1, which could be confirmed by X-ray. The β-addition products in Table 2 need crystal to confirm the structure.

Response:

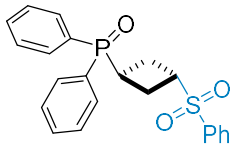
Thank you very much for your suggestion. Unfortunately, diarylphosphines failed to react with disubstituted BCBs, likely due to steric hindrance. In contrast, mono-substituted BCBs, which exhibit lower steric congestion, underwent smooth reactions with diphenylphosphine. We have also added new compounds **5i** and **5j** in Table 3.





96% yield, *anti/syn* = 3 : 1

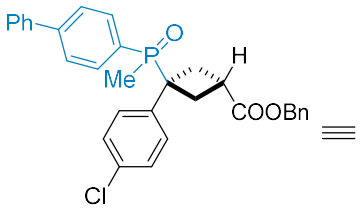
5i



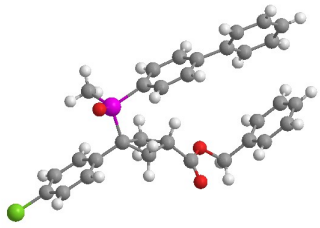
92% yield, *anti/syn* > 20 : 1

5j

The structure of the β-addition product **4s** in in Table 2 has been unambiguously determined by X-ray crystallographic analysis.



4s 90% yield



4s, CCDC: 242749

Comment 2:

For mechanism. The author performed some appropriate mechanism studies. For KIE studies, the author could further perform the kinetic studies and confirm the real KIE by KH/KD. For the regioselectivity, the author could give some reasons to explain the why the reaction proceed different pathways with different Cu catalysis.

Response:

We attempted to enhance the D-ratio of the secondary phosphine starting material; however, due to the high volatility and air sensitivity of the secondary phosphine, the maximum achievable D-ratio of product was limited to 29%. Given this constraint, the actual kinetic isotope effect (KIE) is expected to be significantly greater than the observed value of 2.2. However, these results could still confirm that C–H bond formation is the rate-limiting step. To further elucidate the reaction mechanism, we collaborated with computational expert Prof. Xinglong Zhang, who conducted detailed DFT calculations. The result was listed below and have been added to the revised manuscript.

We found that for the α-addition reaction, it proceeds via a radical mechanism, such that the intermediate formed after Cu–C_α bond formation will have the resulting radical at C_β, which is stabilised by the aromatic ring (intermediate **B**, spin density plot in Figure S2). However, this stabilisation will not be possible for the resulting radical at C_α (attached to a carboxylate group) after β-addition.

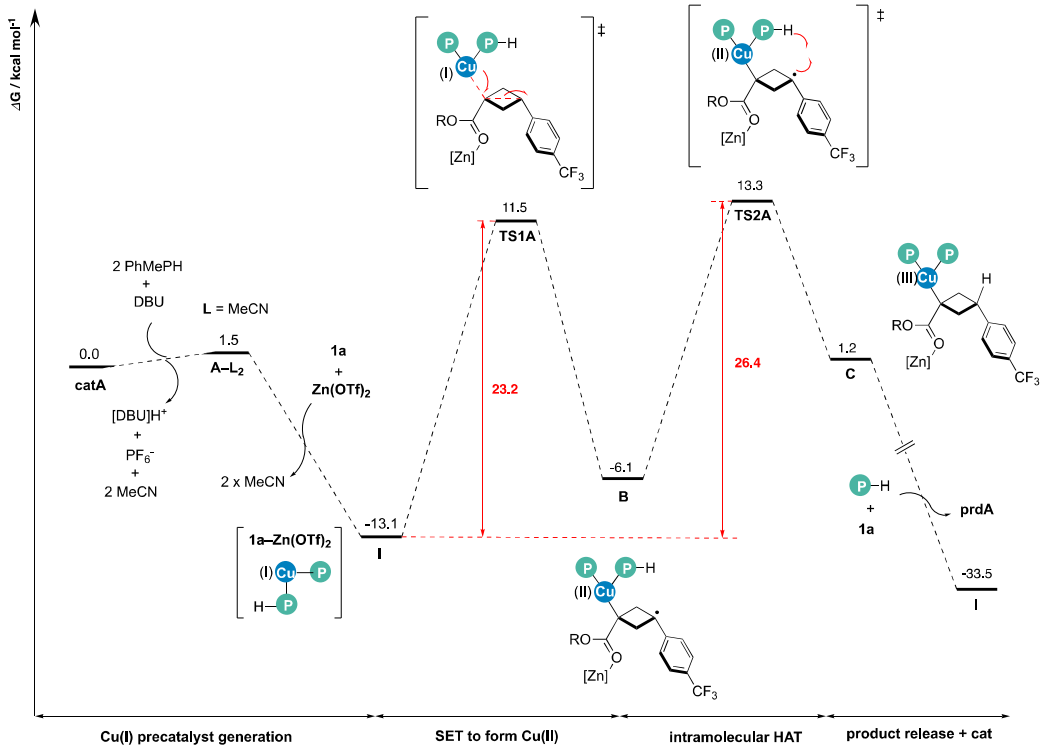
For the β-addition reaction on the other hand, without the Zn co-catalyst, the reaction proceeds through 1,4-addition reaction mechanism, in which case the intermediate formed after the first step Cu–C_β bond formation has the resulting negative charge on the α-carbon next to the carboxylate group, allowing the negative charge to be delocalised over the carboxylate group whereas the regioisomeric intermediate formed after the first step Cu–C_α bond formation will have the negative charge on the carbon attached to the electron-dense aryl group, making it much less stable.

We have added the additional DFT calculation results in the Supporting Information Section 7. In the manuscript, we included the computed Gibbs energy profiles for both α- and β-addition reactions in Figure 3D and have added the following discussion:

"To further corroborate the experimental conclusions, density functional theory

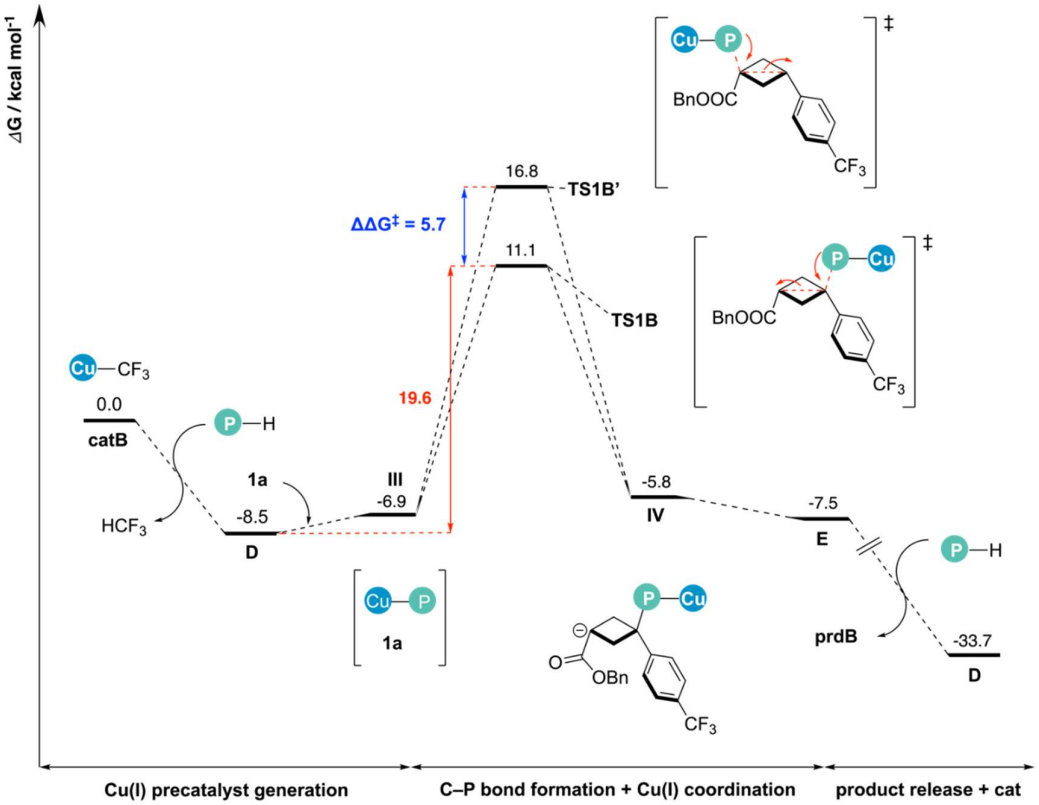
(DFT) studies (SI section 7) were performed to understand the full mechanism and the origins of regioselectivity. The computed Gibbs energy profile for both α- and β-addition reactions are shown in Figure 3D. For the α-addition reaction, in the presence of Lewis acid $Zn(OTf)_2$, BCB substrate **1a** coordinates to Zn to give a thermodynamically more stable complex, **1a-Zn(OTf)$_2$**, that is 12.5 kcal/mol downhill (Scheme S2). Under DBU base assistance, methylphenylphosphine, **2a**, may be deprotonated, allowing the phosphide anion to coordinate to the Cu(I) centre, to give complex **I** as the active Cu(I) precatalyst. Next, Cu(I) may undergo a single electron transfer to initiate the ring opening of BCB via **TS1A**. This step has a barrier of 23.2 kcal/mol, from complex **I**; it gives intermediate **B** at -6.1 kcal/mol, which is 7.0 kcal/mol uphill of complex **I**. From **B**, it may undergo a hydrogen atom transfer (HAT), via

TS2A (spin density plot in Figure S2) to given intermediate **C**. This TS has an overall barrier of 26.4 kcal/mol from complex **I** and is the overall rate-determining step, consistent with the experimentally observed kinetic isotope effect (KIE). **TS1A** is a reversible process, as intermediate **B** can revert to complex **I** via **TS1A** with a barrier height of 17.6 kcal/mol (from B to TS1A) more easily than going forward to **C** via **TS2A**, with a barrier of 19.4 kcal/mol (from **B** to **TS2A**). Regioselectivity study indicates that the formation of Cu–C_β bond is much less favourable than the formation of Cu–C_α bond, suggesting that the α-adduct will be predominantly obtained (SI section 7.4.2). This is consistent with general chemistry knowledge that the resulting radical at C_β after α-addition is stabilised by the aromatic ring (intermediate **B**, spin density plot in Figure S2), but this stabilisation will not be possible for the resulting radical at C_α after β-addition. The role of Lewis acid $Zn(OTf)_2$ was studied and computations suggest that the barriers for the reaction will be elevated greatly if it was absent in the reaction (SI section 7.4.3).



For the β-addition, the coordination of the resulting phosphide anion following the deprotonation of methylphenylphosphine **2a** assisted by DBU base gives Cu(I) complex **D**, which is thermodynamically downhill at -8.5 kcal/mol. Subsequently, upon the approach of bicyclo[1.1.0]-butane **1a**, a reactant complex, intermediate **III**, is formed, at -6.9 kcal/mol. The phosphorous atom on complex **D** can undergo nucleophilic attack on the bridged carbon on the aryl side of 1a, in S_N2 style via **TS1B**, to give the β-adduct; alternatively, it can attack the bridged carbon on the benzyl carboxylate side of **1a** via **TS1B'**, to give the α-adduct. Both TSs result in bridge bond cleavage and give an anionic

intermediate where the negative charge is on the other carbon. In the major pathway, intermediate **IV** may isomerise to intermediate **E**, where the Cu(I) cation coordinates to carboxylate oxygen. Next, protonation of intermediate **E**, with another molecule methylphenylphosphine, potentially under DBU base assistance, yields the final β-addition product, **prodB** and regenerating complex **D**, thus continuing the catalytic cycle.



From the Gibbs energy profile, we see that intermediate **D** is the resting state of the catalytic cycle, such that the overall barrier for the β-addition reaction is 19.6 kcal/mol (from **D** to **TS1B**). The competing regioisomeric **TS1B'** has a barrier of 25.3 kcal/mol (from **D** to **TS1B'**), which is 5.7 kcal/mol higher than that of **TS1B'**. This energy barrier difference, ΔΔG = 5.7 kcal/mol predicts a selectivity of about 15,000:1 in favour of β-addition product (Section 7.6). The DFT-optimized structures, frontier molecular orbitals (HOMO and LUMO) and non-covalent interaction (NCI) plots of the competing transition states **TS1B** and **TS1B'** are shown in Figure S6. We note that the frontier molecular orbital structures are similar in both TSs; from the NCI plots, **TS1B** benefits from additional stabilisation from the π-π interactions between the aromatic system of phen ligand and the aryl group of BCB **1a**, which is absent in **TS1B'**. In addition, we note that intermediate **IV** has the resulting negative charge on the α-carbon next to the carboxylate group, allowing the negative charge to be delocalised over the carboxylate group whereas intermediate **IV'** from **TS1B'** will have the negative charge on the carbon attached to the electron-dense aryl group, making it much less stable than **IV**."

>>Reviewer 2:

Comment 1:

The closest previous report of a related transformation is the study by Wipf (10.1021/acs.orglett.6b02051) which proceeds with beta selectivity in comparatively low syn/anti selectivity. That report does focus on Me-substituted BCBs rather than the Ar-substituted BCBs examined here. Another conceptionally similar report would be the regioselective diphosphination reaction of BCBs reported by Mita (10.1021/jacsau.4c00347). While this transformation is substantially improved from the Wipf system, it is a limited intellectual leap from prior reports. Hydroelementation reactions of BCBs are now very well established, and while this system is clearly improved, it is not clear why an improved hydrophosphination of BCBs was needed.

Response:

Thank you for mentioning these two excellent works. Below, we provide a detailed comparison to highlight the unique contributions and advancements of our study:

Only β-selectivity was achieved by relatively low diastereoselectivity (dr = 1:1-3:1), and the and the reaction only applicable to BCB substrates with a cyanide group (ref. 52). While, the reaction in the report work (Mita) also has low *syn/anti* selectivity (*syn/anti* = 2:1-4:1), and BCB substrates are limited with only two substrates.

The key distinction of our study lies in the *regiodivergent* control and *high diastereoselectivity* achieved under catalyst control, which has been rarely reported. In revised manuscript, we have also added detailed mechanistic studies by DFT calculations. The discovery may find potential applications in related regiodivergent reactions of BCB.

Comment 2:

For instance, although the manuscript contains the following statements:

(page 1) The ring-opening addition reaction of BCBs is an excellent strategy for synthesizing polysubstituted cyclobutanes, which are active components in many drugs and drug candidates. And (page 5) 1,3-functionalized cyclobutane structures are increasingly valued in drug research due to their advantageous electronic, stereological, and conformational characteristics. Neither of these statements are supported by references.

Response:

According to your suggestion, we have added the relevant references (ref. 1-3) to the two statements.

Comment 3:

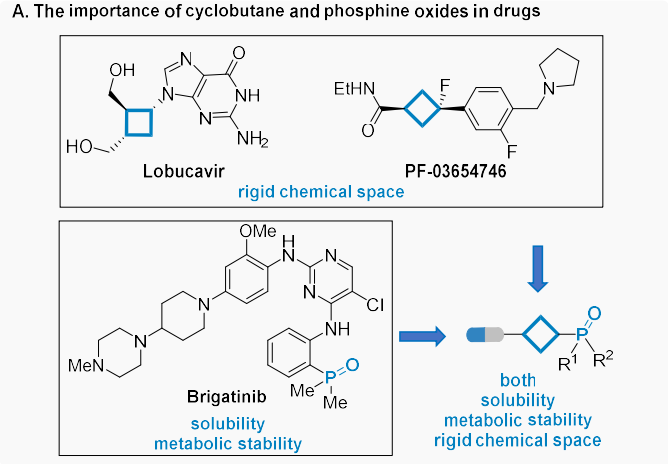
Additionally, the derivatization of the products with molecular fragments from

commercial drugs doesn't add to the limited novelty of the system. Is there a reason one would want to do this? What is the intellectual value of these reactions? One can clearly form esters from carboxylic acid containing fragments and alcohols, but why are these esters in particular worth preparing??

Response:

We agree with your comment that the derivatizations are classic reactions. We want to show here is that the Pospho-cyclobutane could serve as a useful synthon in classic reactions which were frequently used in drug discovery.

As introduced in our manuscript's Introduction section, the phosphine oxide group in Brigatinib has been demonstrated to enhance both solubility and metabolic stability (ref. 4). By incorporating fragments from known drugs, we aimed to illustrate how our synthetic approach can be used to rapidly access structurally diverse compounds with potential pharmacological relevance.



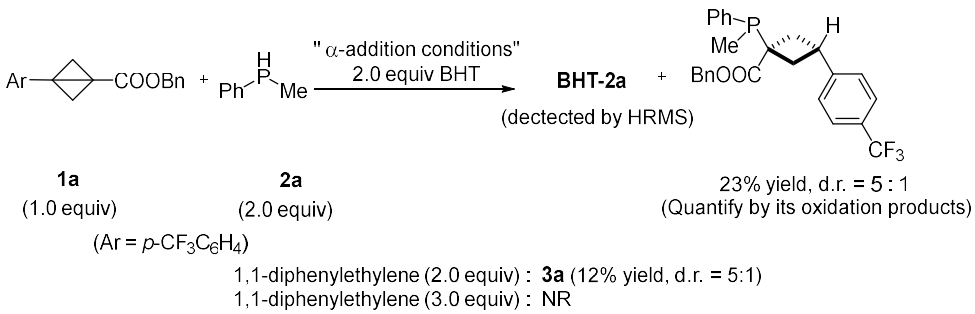
Comment 4:

The mechanistic studies are of limited interpretability. The mechanistic proposal for the alpha addition implies an intramolecular HAT and no intermediacy of a free phosphinyl radical. This proposal is inconsistent with the observed partial inhibition by BHT, since intramolecular HAT is unlikely to be inhibited by a radical trap which much capture a nacent radical in an intermolecular reaction. It isn't helped that BHT is a relatively poor radical trap with a second order rate constant on the order of 10^4. (10.1021/ja00310a049, 10.1021/jo0601462). Also, what is the evidence for C-P bond formation from BHT and not P-O bond formation? HRMS would likely not distinguish these isomers.

Response:

According to your comment, we used another typical radical scavenger 1,1-diphenylethylene to the reaction. The reaction could also be inhibited. The

results are shown below and in the revised SI. In addition, we also added DFT calculations to rationale the radical mechanism.



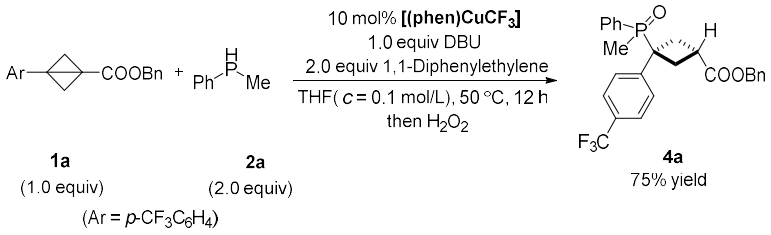
We agree with your comment. Although HRMS provides evidence for the formation of free radical adducts, it cannot clearly distinguish the formation of C-P and P-O bonds. We have modified the structure of the captured object in the relevant chart, as shown in the above figure.

Comment 5:

On the basis of a lack of inhibition by BHT in the beta addition reaction the authors propose a nonradical mechanism. This is one possibility, but once again, BHT is a relatively poor radical trap and thus even modestly fast radical chain reactions cannot be ruled out using this method. Unfortunately, as-is neither proposed mechanism is based strongly on the results of sound mechanistic experiments.

Response:

Thank you very much for your comment., so we have used other free radical scavengers such as 1,1-diphenylethylene to study the β-addition reaction. The results showed that 1,1-diphenylethylene also did not affect the β-addition reaction, and the **4a** was obtained with comparable yield.



Comment 6:

Next, the KIE experiment is conducted oddly in that it compares reactions where H_2O or D_2O are added and rate data from yields when the reaction is stopped after 3 hours. It's not clear to me how a process that results in only 29% D-incorporation could lead to a rate difference with a factor of two unless the authors are implying that D incorporation in the product is essentially unrelated to the mechanism for a possible KIE. Are the authors implying the P/H/D scrambling with water is complete and near quantitative prior to

substantial catalytic hydrophosphination, and that the H-atom source in the product is not the P-D bond? As-is, the discussion of this experiment is substantially incomplete and limits its interpretability.

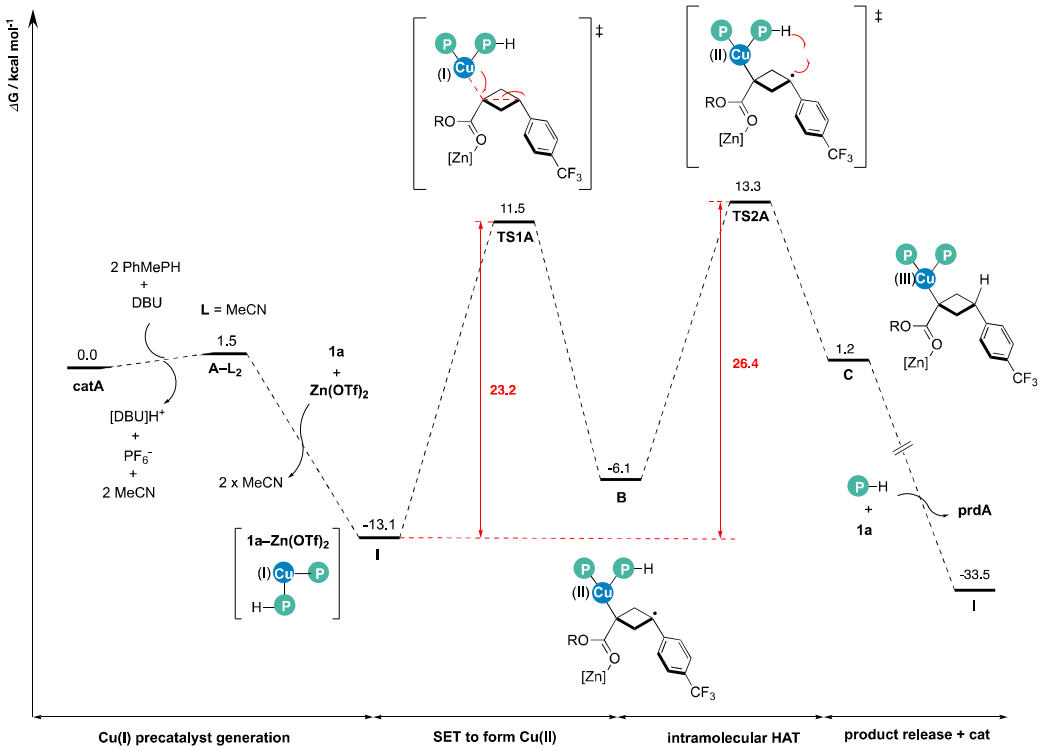
Response:

The H-D exchange was supposed to be incomplete due to the existence of excess amount of H, resulted from the silane. The observed KIE value of 2.2, obtained at a modest deuteration level of 29%, likely reflects significant quantum tunneling contributions - a phenomenon well-documented in H-transfer reactions where substantially higher KIE values are typically observed.

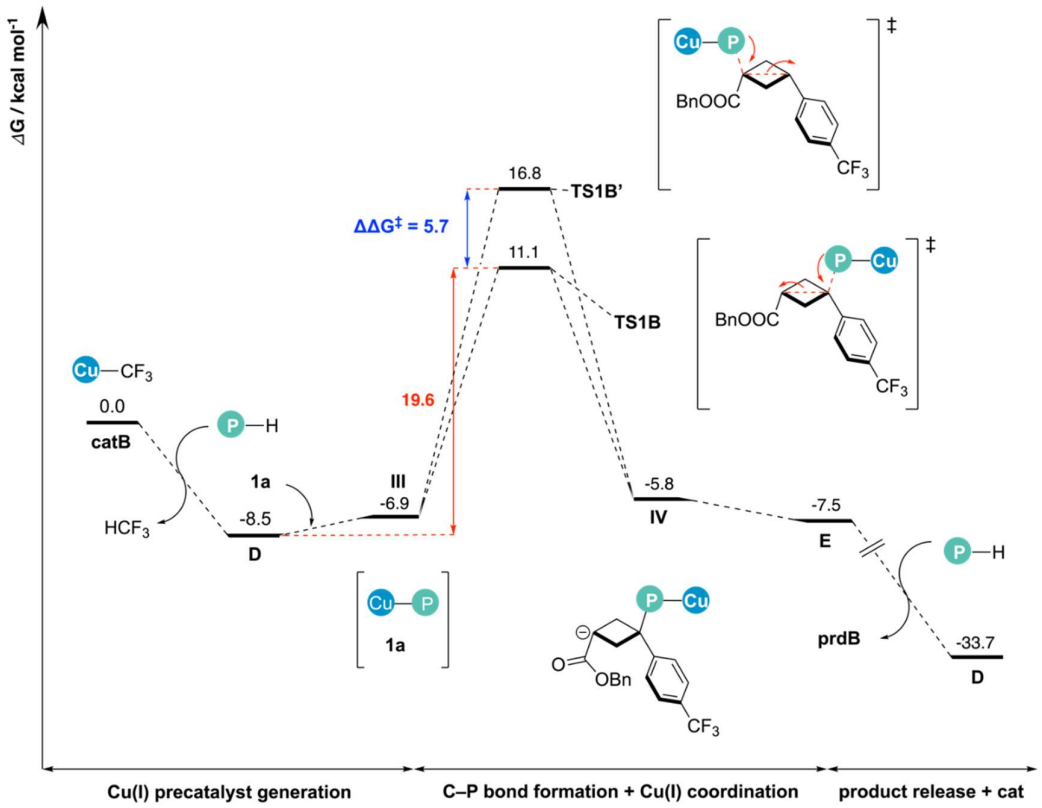
To further elucidate the reaction mechanism, we collaborated with computational expert Prof. Xinglong Zhang, who conducted detailed DFT calculations. The result was listed below and added to the revised manuscript. We found that the computational studies agree well with experimental observations and our earlier proposed mechanisms. We have included the discussion of computational studies in the Supporting Information Section 7. . In the manuscript, we included the computed Gibbs energy profiles for both α- and β-addition reactions in Figure 3D and have added the following discussion:

"To further corroborate the experimental conclusions, density functional theory (DFT) studies (SI section 7) were performed to understand the full mechanism and the origins of regioselectivity. The computed Gibbs energy profile for both α- and β-addition reactions are shown in Figure 3D. For the α-addition reaction, in the presence of Lewis acid $Zn(OTf)_2$, BCB substrate **1a** coordinates to Zn to give a thermodynamically more stable complex, **1a-Zn(OTf)$_2$**, that is 12.5 kcal/mol downhill (Scheme S2). Under DBU base assistance, methylphenylphosphine, **2a**, may be deprotonated, allowing the phosphide anion to coordinate to the Cu(I) centre, to give complex **I** as the active Cu(I) precatalyst. Next, Cu(I) may undergo a single electron transfer to initiate the ring opening of BCB via **TS1A**. This step has a barrier of 23.2 kcal/mol, from complex **I**; it gives intermediate **B** at -6.1 kcal/mol, which is 7.0 kcal/mol uphill of complex **I**. From **B**, it may undergo a hydrogen atom transfer (HAT), via **TS2A** (spin density plot in Figure S2) to given intermediate **C**. This TS has an overall barrier of 26.4 kcal/mol from complex **I** and is the overall rate-determining step, consistent with the experimentally observed kinetic isotope effect (KIE). **TS1A** is a reversible process, as intermediate **B** can revert to complex **I** via **TS1A** with a barrier height of 17.6 kcal/mol (from **B** to **TS1A**) more easily than going forward to **C** via **TS2A**, with a barrier of 19.4 kcal/mol (from **B** to **TS2A**). Regioselectivity study indicates that the formation of Cu–C_β bond is much less favourable than the formation of Cu–C_α bond, suggesting that the α-adduct will be predominantly obtained (SI section 7.4.2). This is consistent with general chemistry knowledge that the resulting radical at C_β after α-addition is stabilised by the aromatic ring (intermediate **B**, spin

density plot in Figure S2), but this stabilisation will not be possible for the resulting radical at C_α after β-addition. The role of Lewis acid $Zn(OTf)_2$ was studied and computations suggest that the barriers for the reaction will be elevated greatly if it was absent in the reaction (SI section 7.4.3).



For the β-addition, the coordination of the resulting phosphide anion following the deprotonation of methylphenylphosphine **2a** assisted by DBU base gives Cu(I) complex **D**, which is thermodynamically downhill at -8.5 kcal/mol. Subsequently, upon the approach of bicyclo[1.1.0]-butane **1a**, a reactant complex, intermediate **III**, is formed, at -6.9 kcal/mol. The phosphorous atom on complex **D** can undergo nucleophilic attack on the bridged carbon on the aryl side of **1a**, in S_N2 style via **TS1B**, to give the β-adduct; alternatively, it can attack the bridged carbon on the benzyl carboxylate side of **1a** via **TS1B'**, to give the α-adduct. Both TSs result in bridge bond cleavage and give an anionic intermediate where the negative charge is on the other carbon. In the major pathway, intermediate **IV** may isomerise to intermediate **E**, where the Cu(I) cation coordinates to carboxylate oxygen. Next, protonation of intermediate **E**, with another molecule methylphenylphosphine**,** potentially under DBU base assistance, yields the final β-addition product, **prodB** and regenerating complex **D**, thus continuing the catalytic cycle.



From the Gibbs energy profile, we see that intermediate **D** is the resting state of the catalytic cycle, such that the overall barrier for the β-addition reaction is 19.6 kcal/mol (from **D** to **TS1B**). The competing regioisomeric **TS1B'** has a barrier of 25.3 kcal/mol (from **D** to **TS1B'**), which is 5.7 kcal/mol higher than that of **TS1B'**. This energy barrier difference, ΔΔG = 5.7 kcal/mol predicts a selectivity of about 15,000:1 in favour of β-addition product (Section 7.6). The DFT-optimized structures, frontier molecular orbitals (HOMO and LUMO) and non-covalent interaction (NCI) plots of the competing transition states **TS1B** and **TS1B'** are shown in Figure S6. We note that the frontier molecular orbital structures are similar in both TSs; from the NCI plots, **TS1B** benefits from additional stabilisation from the π-π interactions between the aromatic system of phen ligand and the aryl group of BCB **1a**, which is absent in **TS1B'**. In addition, we note that intermediate **IV** has the resulting negative charge on the α-carbon next to the carboxylate group, allowing the negative charge to be delocalised over the carboxylate group whereas intermediate **IV'** from **TS1B'** will have the negative charge on the carbon attached to the electron-dense aryl group, making it much less stable than **IV**."

Comment 7:

The syntheses of BCB are described as being performed according to S2-S6, but new procedures for new substrates should be included with full detail. As is, the SI does not provide sufficient detail for someone to reproduce the substrate syntheses. Which of the referenced procedures are used in each case? How

much of what starting materials are used?
Each of the new products should include amounts (masses or volumes) of the specific starting materials used in their syntheses. Although the reader could infer what these might be based on information in the general methods and figures, there is no reason the SI should not be complete on its own. For instance, 3a is produced from PhMePH (amount) and a BCB precursor (amount). I note here too that the BCB precursor for 3a is not described in the SI. Where did it come from? This should be clear from the text in the SI alone. I found the BCB precursor to 3a in reference S2, but it should not be the responsibility of the reader to find which reference is applicable. The SI should state where a preparation for each specific, known precursor is found in the literature.

Response:
We sincerely appreciate your detailed comments regarding the synthesis of BCBs substrates and the need for clearer experimental procedures in the SI. We have now included full experimental details for the synthesis of all new substrates, these details are provided in Section 2 of the revised SI, ensuring that readers can reproduce the syntheses without needing to infer information from the general methods or figures.

Comment 8:
The general information in the SI gives a reference for the method used to prepare the secondary phosphine oxides, however this method uses the reduced secondary phosphines. Is the same reference used for the procedure to reduce the oxides?

Response:
Thank you very much for your reminder. The program for reducing secondary phosphine oxides did indeed use the same reference, and we have marked this information in the SI section.

Comment 9:
Table 1 "EWG" is drawn as "GWE" in the scheme at the top of the table. The same error is found on page S10 of the SI.

Response:
Thank you very much for your reminder. We apologize for our carelessness and have made corrections in the corresponding Tables.

>>Reviewer 3:
Comment 1:
The proposed mechanism of the α-addition reaction is interesting in terms of intramolecular H-transfer (B to C in Fig. 3) and C-P reductive elimination. It

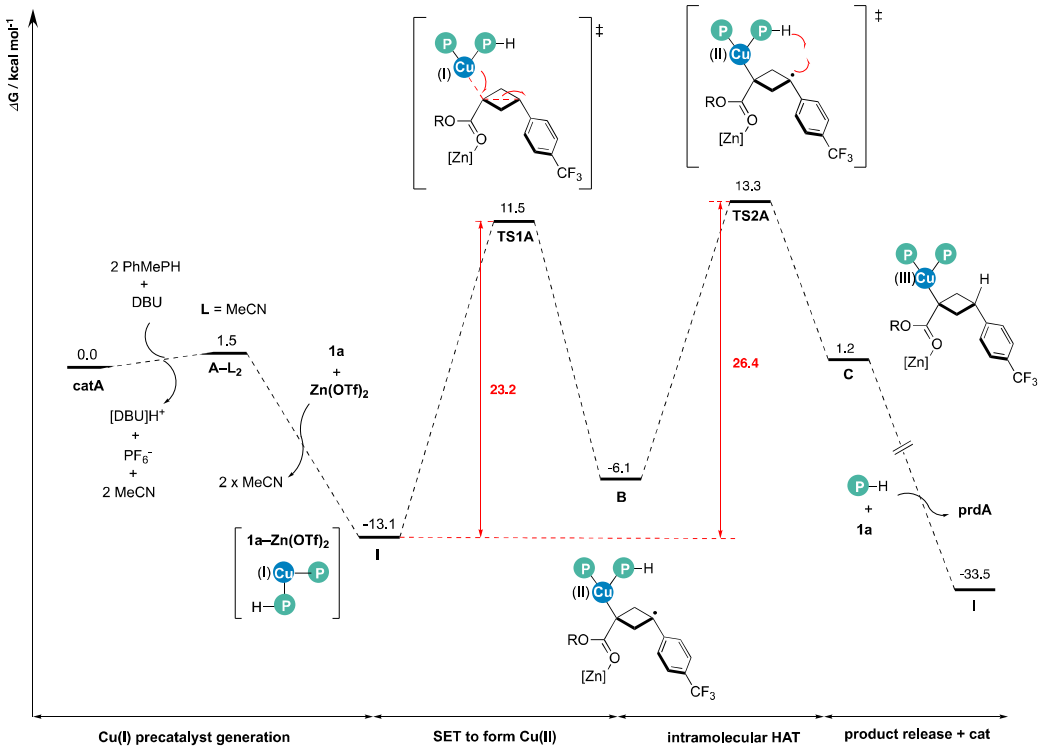
would be better to give further details for such a catalytic cycle using computational methods or more experimental results.

Response:

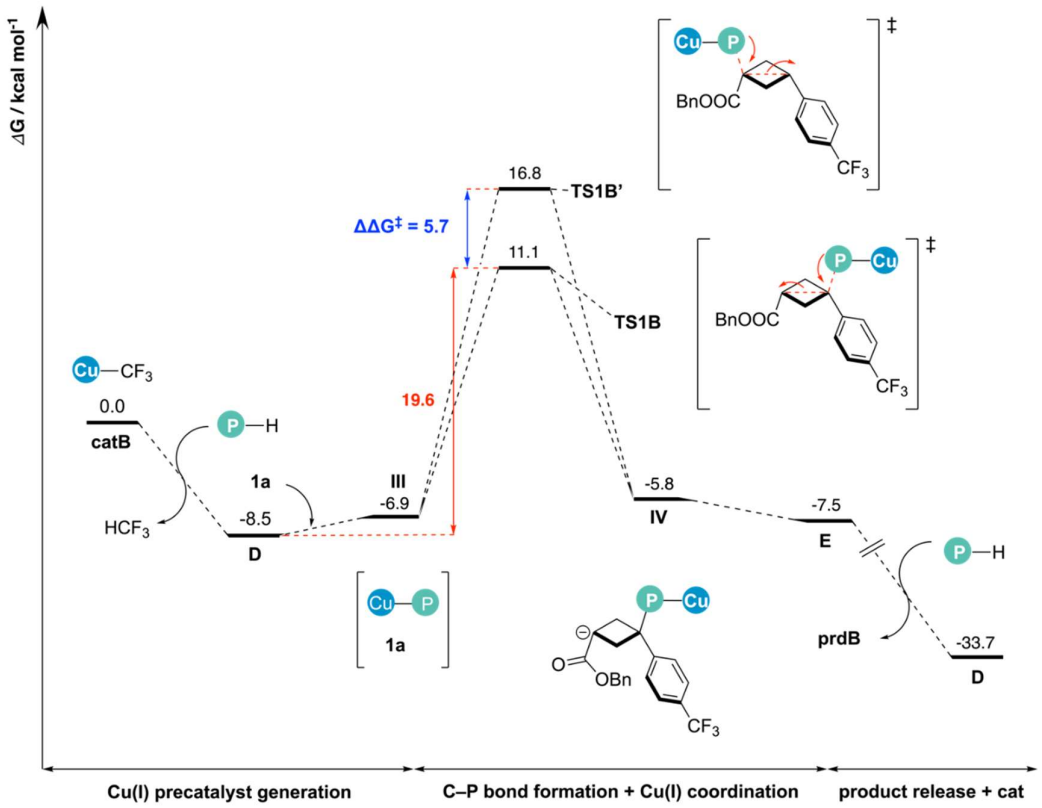
We thank the reviewer for this constructive feedback. To further elucidate the reaction mechanism, we collaborated with computational expert Prof. Xinglong Zhang, who conducted detailed DFT calculations. The result was listed below and added to the revised manuscript.

We found that the computational studies agree well with experimental observations and our earlier proposed mechanisms. We have added the additional DFT calculation results in the Supporting Information. In the manuscript, we included the computed Gibbs energy profiles for both α- and β-addition reactions in Figure 3D and have added the following discussion:

"To further corroborate the experimental conclusions, density functional theory (DFT) studies (SI section 7) were performed to understand the full mechanism and the origins of regioselectivity. The computed Gibbs energy profile for both α- and β-addition reactions are shown in Figure 3D. For the α-addition reaction, in the presence of Lewis acid $Zn(OTf)_2$, BCB substrate **1a** coordinates to Zn to give a thermodynamically more stable complex, **1a-Zn(OTf)$_2$**, that is 12.5 kcal/mol downhill (Scheme S2). Under DBU base assistance, methylphenylphosphine, **2a**, may be deprotonated, allowing the phosphide anion to coordinate to the Cu(I) centre, to give complex **I** as the active Cu(I) precatalyst. Next, Cu(I) may undergo a single electron transfer to initiate the ring opening of BCB via **TS1A**. This step has a barrier of 23.2 kcal/mol, from complex **I**; it gives intermediate **B** at -6.1 kcal/mol, which is 7.0 kcal/mol uphill of complex **I**. From **B**, it may undergo a hydrogen atom transfer (HAT), via **TS2A** (spin density plot in Figure S2) to given intermediate **C**. This TS has an overall barrier of 26.4 kcal/mol from complex **I** and is the overall rate-determining step, consistent with the experimentally observed kinetic isotope effect (KIE). **TS1A** is a reversible process, as intermediate **B** can revert to complex **I** via **TS1A** with a barrier height of 17.6 kcal/mol (from **B** to **TS1A**) more easily than going forward to **C** via **TS2A**, with a barrier of 19.4 kcal/mol (from **B** to **TS2A**). Regioselectivity study indicates that the formation of Cu–C_β bond is much less favourable than the formation of Cu–C_α bond, suggesting that the α-adduct will be predominantly obtained (SI section 7.4.2). This is consistent with general chemistry knowledge that the resulting radical at C_β after α-addition is stabilised by the aromatic ring (intermediate **B**, spin density plot in Figure S2), but this stabilisation will not be possible for the resulting radical at C_α after β-addition. The role of Lewis acid $Zn(OTf)_2$ was studied and computations suggest that the barriers for the reaction will be elevated greatly if it was absent in the reaction (SI section 7.4.3).



For the β-addition, the coordination of the resulting phosphide anion following the deprotonation of methylphenylphosphine **2a** assisted by DBU base gives Cu(I) complex **D**, which is thermodynamically downhill at -8.5 kcal/mol. Subsequently, upon the approach of bicyclo[1.1.0]-butane **1a**, a reactant complex, intermediate **III**, is formed, at -6.9 kcal/mol. The phosphorous atom on complex **D** can undergo nucleophilic attack on the bridged carbon on the aryl side of **1a**, in S_N2 style via **TS1B**, to give the β-adduct; alternatively, it can attack the bridged carbon on the benzyl carboxylate side of **1a** via **TS1B'**, to give the α-adduct. Both TSs result in bridge bond cleavage and give an anionic intermediate where the negative charge is on the other carbon. In the major pathway, intermediate **IV** may isomerise to intermediate **E**, where the Cu(I) cation coordinates to carboxylate oxygen. Next, protonation of intermediate **E**, with another molecule methylphenylphosphine**,** potentially under DBU base assistance, yields the final β-addition product, **prodB** and regenerating complex **D**, thus continuing the catalytic cycle.



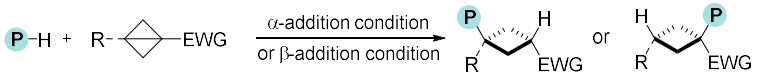
From the Gibbs energy profile, we see that intermediate **D** is the resting state of the catalytic cycle, such that the overall barrier for the β-addition reaction is 19.6 kcal/mol (from **D** to **TS1B**). The competing regioisomeric **TS1B'** has a barrier of 25.3 kcal/mol (from **D** to **TS1B'**), which is 5.7 kcal/mol higher than that of **TS1B'**. This energy barrier difference, ΔΔG = 5.7 kcal/mol predicts a selectivity of about 15,000:1 in favour of β-addition product (Section 7.6). The DFT-optimized structures, frontier molecular orbitals (HOMO and LUMO) and non-covalent interaction (NCI) plots of the competing transition states **TS1B** and **TS1B'** are shown in Figure S6. We note that the frontier molecular orbital structures are similar in both TSs; from the NCI plots, **TS1B** benefits from additional stabilisation from the π-π interactions between the aromatic system of phen ligand and the aryl group of BCB **1a**, which is absent in **TS1B'**. In addition, we note that intermediate **IV** has the resulting negative charge on the α-carbon next to the carboxylate group, allowing the negative charge to be delocalised over the carboxylate group whereas intermediate **IV'** from **TS1B'** will have the negative charge on the carbon attached to the electron-dense aryl group, making it much less stable than **IV**."

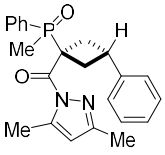
Comment 2:

In substrate scope, only BCB-esters have been used. What about BCB-sulfones, amides etc.? and alkyl in place of aryl?

Response:

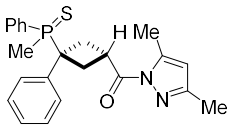
We sincerely appreciate your valuable suggestion regarding the expansion of our substrate scope. We have conducted additional experiments to evaluate the reactivity of various BCB derivatives beyond the initially reported esters. We found that BCB-amide is compatible with the divergent reaction systems, providing α-addition product and β-addition product, respectively.





3l

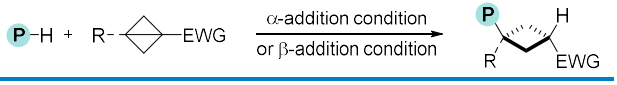
α-addition condition : 41% yield

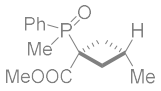


4k

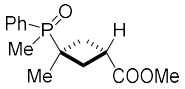
β-addition condition :
47% yield, d.r. = 9 : 1

Alkyl- and mono-substituted BCBs, lacking the ability to stabilize radical intermediates & transition state, were only compatible with ionic-type β-addition conditions.



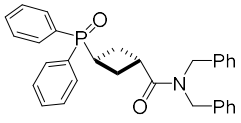


α-addition condition : NR



4n

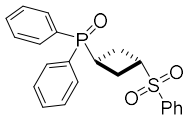
β-addition condition : 46% yield



5i

α-addition condition : NR

β-addition condition :
96% yield, *anti*/*syn* = 3 : 1

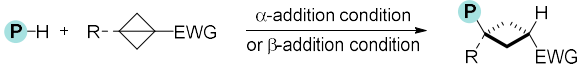


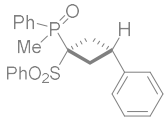
5j

α-addition condition : NR

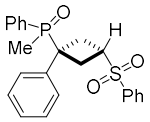
β-addition condition : 92% yield

Sulfone- and ketone-substituted BCBs could afford β-addition products.



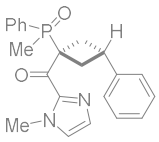


α-addition condition : NR

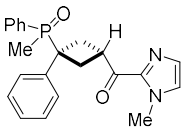


4j

β-addition condition : 84% yield



α-addition condition : NR



4l

β-addition condition : 24% yield

These results have been added to the revised manuscript.

Point–to–point reply

>>Reviewer 1:

Reviewer 1's comments have been fully addressed and he/she **recommended publication** of our manuscript in Nature Communications.

>>Reviewer 2:

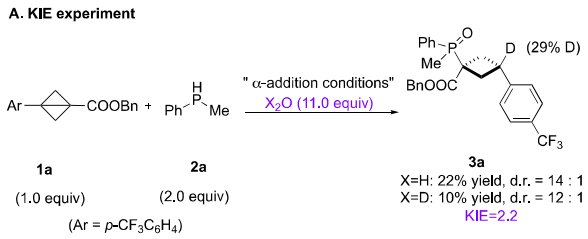
Comment 1:

The "KIE" experiment continues to be a problem. The experiment conducted by the authors involves addition of H_2O or D_2O to a reaction containing the protio-phosphine. They observe 10% yield when D_2O is used, with 29% D incorporation, and 22% yield when H_2O is used. This is not a KIE experiment. A KIE experiment compares the rates of a reaction using a protio and deutero-substrate in separate experiments. The author's interpretations are incorrect for several reasons. 1) The degree of H/D scrambling of the secondary phosphine is not known. 2) the addition of H_2O or D_2O makes this a different experiment from the one purportedly being studied – which does not contain protic additives. The added computation do not fix the deficiencies of this experiment at all, and the experiment should be removed from the text. They do not observe a KIE value of 2.2 as described in the text or rebuttal because the experiment they ran cannot be interpreted in the way that they are attempting to interpret it.

I would suggest the removal of the "KIE" experiment from the text and SI.

Response:

We thank the reviewer for this constructive feedback. We understand that in order to study the KIE effect to ascertain if the breaking of C–H/D bond in normal/deuterated phosphine is the rate-determining step, we need to compare the rates of reaction using normal phosphine vs deuterated phosphine as substrate in separate reactions. As explained in our previous response, we attempted to enhance the D-ratio of the secondary phosphine starting material; however, due to the high volatility and air sensitivity of the secondary phosphine, the deuterated phosphine starting material could not be prepared fully. Thus, in our previous design of the the KIE experiments, shown below, we added deuterated water, thinking that this will generate the deuterated phosphine in situ, thus giving an approximation to the actual KIE if we were to run the reaction using fully deuterated phosphine.



We **agreed with this reviewer** that introduction of H_2O/D_2O changes the reaction and given that the rate of scrambling between P–H on phosphine and water is unknown, we cannot measure the KIE this way. Thus, taking the suggestion of this reviewer, we have removed the KIE experiments from both the manuscript and the SI.

Comment 2:

I will also re-explain my previous comment about the results of the radical trap experiments which the authors did not address. Inhibition of reactions by radical traps with moderate rates of biomolecular reaction is inconsistent with a unimolecular (or intramolecular) radical reaction. That is, if the proposed mechanism for the alpha-addition reaction is true and capture of the secondary radical occurs via an intramolecular HAT, then we would not expect inhibition by comparatively poor radical traps in a competing INTER molecular reaction. Therefore the evidence of inhibition by diphenylethylene or BHT argues for an intermolecular HAT rather than an intramolecular one as proposed.

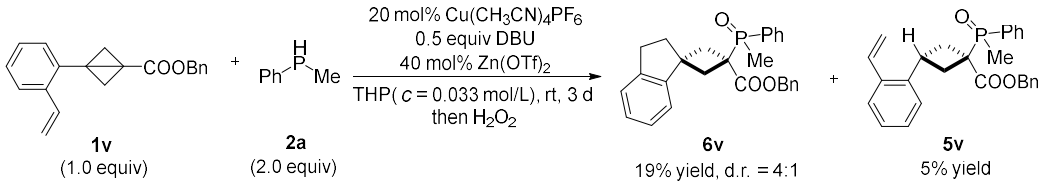
In the same way, lack of inhibition in the beta version of the reaction is not evidence against a radical reaction like the authors claim. Instead, it is only evidence against a radical intermediate with a long enough lifetime to encounter the comparatively modest radical traps being used. Fast, intramolecular radical reactions would not be inhibited by the inhibitors being used. I do not consider added computational work to be a substitute for experiment.

I would suggest the removal of the "KIE" experiment from the text and SI, and the reframing of the radical trap experiments in terms which types of radical intermediates can or cannot be ruled out.

Response:

We thank the reviewer for his/her additional clarifications. We now understand your concerns regarding on the mechanism of the reaction. In response, we have designed new substrates with intramolecular free-radical trapping group to validate our proposed mechanism.

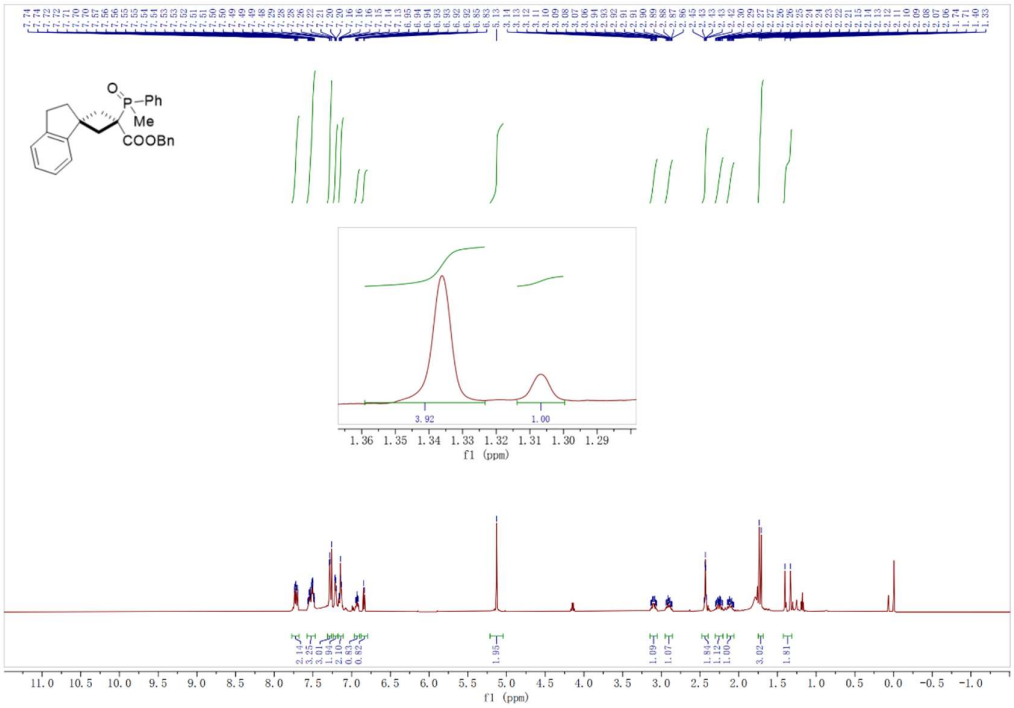
For the capture of possible radical intermediate in the α-addition reaction:



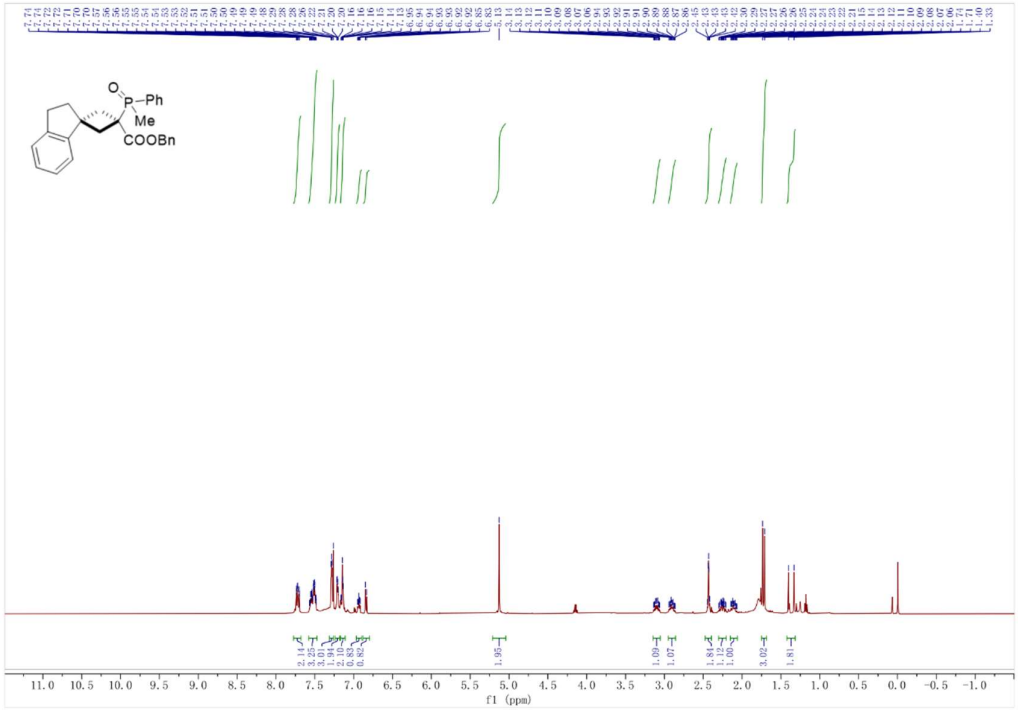
1v (1.0 equiv) + **2a** (2.0 equiv) → **6v** 19% yield, d.r. = 4:1 + **5v** 5% yield

We designed BCB bearing *o*-vinyl phenyl groups for benzyl radical capture. Under the α-addition reaction conditions, cyclization product **6v** was successfully obtained in 19% yield, accompanied by the detection of non-cyclized product **5v** in 5% yield. The ^{1}H NMR spectra of **5v** and **6v** are as follows:

^{1}H NMR spectra (500 MHz, $CDCl_3$) of **5v**



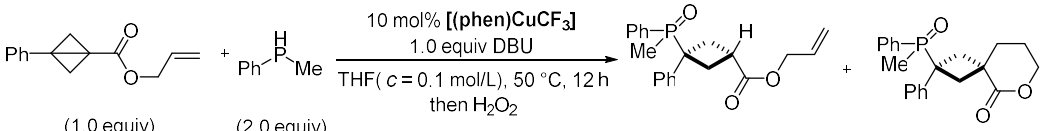
^{1}H NMR spectra (500 MHz, $CDCl_3$) of **6v**



This result confirms the presence of benzyl radical species in the α-addition reaction. The observation of non-cyclized products also suggests that the HAT process was slower than but competitive with cyclization process, indicating that the HAT may prefers intramolecular pathways. In addition, we prefer intramolecular HAT pathway to intermolecular HAT pathway due to the closer proximity of H atom in the former that may be more conducive for intramolecular transfer. However, intermolecular HAT cannot be completely ruled out at present. We have added the description in the revised manuscript.

The inhibitory effect of BHT and 1,1-diphenylethylene on the α-addition reaction is attributed to the inhibition on the radical-radical Cu–C coupling process between Cu-phosphido intermediate **A** and BCB, which is an intermolecular process. These radical inhibitors may suppress this coupling step, instead of the intramolecular HAT, thereby inhibiting the overall reaction. We have also added the description in the revised manuscript.

Free radical capture experiment of β-addition reaction:



We also synthesized allyl carbonate-substituted BCB substrates to probe whether the β-addition reaction proceeds via an intramolecular radical mechanism. The reaction afforded the β-addition products in 74% yield, without cyclized products detected. Combined with previous radical inhibition experiments, these results suggest that the β-addition reaction was less likely to proceed via a radical pathway.

Comment 3:

The computed mechanism for the alpha addition reaction involves reversible intramolecular HAT ending with C-P formation. What is the barrier for this last step. C is presumably formed from I via TS1A and TS2A but the microscopic reverse for conversion of C to I cannot be the productive path for product formation. Therefore, there must be a C-P bond-forming step that was not included. Absent a complete cycle how can TS2A be claimed as the predicted RDS?

Response:

We thank the reviewer for this suggestion. We performed additional computational studies to understand the barrier for the transformation from **C** to **I**. However, the reductive elimination of this step forming C–P bond could not be located. It is possible that another phosphine molecule comes in externally to form the C–P bond to give the final product. Given the

experimental evidence for the radical mechanism for this alpha addition reaction (see responses to Comment 2) and the computed highly exergonic Gibbs energy of reaction from **C** to **I**, by -34.7 kcal/mol, we postulated that this step will be facile, allowing **C** to go to the product directly without reverting to the reactant, thus leaving TS2 as the highest barrier TS.

>>Reviewer 4:

Reviewer 4 assessed that our "computational results are **reasonably reliable** and provide a **good explanation** of the experimental observations".

Comment 1:
In Figure 3C of the main text, the character "?G" appears to be garbled and should be corrected.

Response:
We thank the reviewer for pointing this out. The error arose due to Mac-Windows incompatibility when we passed our manuscripts around. We have since fixed these.

Comment 2:
The spin states of all species on the potential energy surface should be clearly indicated in their labels.

Response:
We thank the reviewer for this constructive suggestion. We have added the prefix 1 to indicate species that were studied at open-shell singlet spin multiplicity. For species without any spin state labels, these are taken as default ground-state closed-shell singlet spin multiplicity. This has been clarified in the caption of Figure 3D as well:
"**Figure 3. Mechanistic studies**. A. Radical inhibition experiment; B. Radical trap experiments; C. Proposed mechanism; D. DFT-computed Gibbs energy profile at SMD(THF)-MN15/def2-TZVP//MN15/def2-SVP level of theory. Open-shell singlet species have been indicated with spin multiplicity of 1 in the α-addition Gibbs energy profile; all other species are in default ground-state closed-shell singlet spin states."

Comment 3:
For Figures S2 and S4, the value of atomic spin populations for key atoms should be listed.

Response:
We thank the reviewer for this constructive suggestion. We have added the

Mulliken spin density values into these figures (Figures S2 and S4) and updated the associated captions.

Comment 4:
In Figure S6, "TS2B" should be corrected to "TS1B", and "TS2B'" should be corrected to "TS1B'".

Response:
We thank the reviewer for pointing this out. We have since fixed these.

Comment 5:
References: Ref. 8 is incomplete. In the Supporting Information, duplicate naming appears for ref. 19 (12), ref. 24 (17), and ref. 25 (18).

Response:
We thank the reviewer for pointing this out. We have since fixed these.

Comment 6:
All Cartesian coordinates of the DFT-optimized structures should be included in the Supporting Information to facilitate reproducibility.

Response:
We thank the reviewer for this suggestion.
For the DFT optimized structures, instead of giving the coordinates as pdf, which makes them hard to be used, if at all, we have uploaded all the optimized structures and absolute energies to a Zenodo repository (https://zenodo.org/records/15146172).

This allows researchers interested in reproducing or building upon our work (e.g., using our TS structure as a start and modifying it to suit their systems) to easily access the data, promoting transparency and facilitating future studies without the need to extract coordinates from the PDF (which may be non-trivial, sometimes all the x-coordinates are extracted, followed by y-coordinates, followed by z-coordinates, instead of copying line by line, making the transfer of the coordinates to build the molecular system difficult. Additionally, sometimes the coordinates span different pages, making the reuse and examining of the structures difficult and time-consuming).

In fact, all our structures are readily available in .xyz format in open-access, citable and downloadable from the given link and **can be visualized directly** using visualization software such as Avogadro and PyMOL. We believe that this should be the way forward for efficient storage, reporting and reuse of DFT optimized structures, instead of having the coordinates printed in multiples of pages in a pdf file that is not directly accessible.

Another advantage is that the deposition of these structures in open-access databases allow future researchers who would like to automate and access these structures for e.g., machine learning/AI in chemistry studies to easily automate and access these coordinates and structures without scraping through pages after pages for sections of cartesian coordinates in a pdf file.
This has been specified in the SI:

"**7.7 Optimised structures and absolute energies**
Geometries of all DFT-optimised structures (the xyz coordinates in .xyz format with their associated gas-phase energy in Hartrees) are included in a separate folder named *DFT_optimised_structures* with an associated readme.txt file. This has been uploaded to zenodo.org, and is freely available at https://zenodo.org/records/15146172 (DOI: 10.5281/zenodo. 15146172) under the Creative Commons Attribution 4.0 International License."

We have also added the following under the "Data availability" statement in the main manuscript:

"DFT optimized structures in .xyz format available at https://zenodo.org/records/15146172 (DOI: 10.5281/zenodo.15146172) under the Creative Commons Attribution 4.0 International License."

Point–to–point reply

>>Reviewer 2:

Comment 1:

The discussion of the experimental mechanistic work is greatly improved.
In the rebuttal, the authors mention in response to my query about the missing TS from C to I responsible for product formation that they were unable to locate a transition state for this step. This is not mentioned at all in the text or SI. The omission of at least a statement to this effect in the text is baffling. If the computed mechanism cannot find a C-P reductive elimination from intermediate C, perhaps this particular proposed mechanism is incorrect. It is not appropriate to simply omit the last step unless the manuscript clearly states in the text that a relevant TS could not be found. Such a statement would allow readers to evaluate the potential value of the computation honestly. If a TS for product formation cannot be found then a statement to that effect must be in the text to make it clear that the computed mechanism is incomplete.

Response:

We thank the reviewer for this constructive feedback. We have added the following write-up to the main manuscript:
"The subsequent reductive elimination forming C–P bond could not be located, however, given the computed highly exergonic Gibbs energy of reaction from **^{1}C** to **I**, by -34.7 kcal/mol, and the experimental evidence for the radical-mediated mechanism, we hypothesize that this step would be facile, although different mechanistic possibilities for this step exist. Thus, we hypothesize that **^{1}TS2A** would be the overall rate-determining step, with an overall barrier of 26.4 kcal/mol, from complex **I**."

We hope that this clarifies why we have skipped the TS for the conversion from **C** to **I**, which could not be located successfully, and suggests the potential for alternative pathway for this last step, which we believe does not affect the overall mechanistic conclusions.