nature portfolio

Peer Review File

Organocatalytic Iminium-Assisted Asymmetric B(sp^2)-to-B(sp^3) Transformation

Corresponding Author: Professor Yonggui Robin Chi

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 study presents a novel organocatalytic strategy for enantioselective synthesis of tetracoordinate boron compounds, addressing the long-standing challenge of constructing chiral B(sp^3) centers. By utilizing an amino-thiourea catalyst, the authors developed a direct asymmetric addition to planar B(sp^2) centers in BN-heterocyclic substrates. The method leverages iminium activation between salicylaldehyde and the catalyst to enable nucleophilic attack on the boron center, followed by iminium exchange to form stereogenic tetracoordinate B(sp^3) products with high optical purity (moderate to excellent yields and enantioselectivities). This represents the first reported B(sp^2)-to-B(sp^3) transformation approach in asymmetric boron chemistry. The synthesized chiral organoboron compounds demonstrate synthetic versatility for generating multifunctional derivatives and exhibit promising photophysical properties and antibacterial activities. Mechanistic insights were supported by computational studies elucidating the catalytic cycle and stereocontrol. This work establishes foundational concepts for boron-centered asymmetric bond formation and expands access to structurally diverse chiral tetracoordinate boron molecules, potentially advancing materials science and medicinal research. I suggest publication of this manuscript in Nat. Commun. after the authors address the following comments regarding the photophysical characterizations.

1. In Figure 6d, the curve labeled as 85% shows an unusual decrease in fluorescence intensity and retesting is recommended.

2. Calculations show that compounds 3a and 3j achieve intersystem crossing via the S1→T2 pathway. Is it possible to provide experimental characterizations to support the calculation results?

3. Figure 6a shows non-normalized absorption spectra, while it is described as normalized absorption spectra in the text.

4. The PLQY measurement has standard errors of <5%. Typically it is not necessary to keep decimals as the measurement cannot be so accurate (Table 2).

5. The discussions on CD and CPL are too concise. More discussions are recommended, for example, by comparing with reported compounds and theoretical calculations.

6. There are several typos and formatting mistakes, such as wrong title for Table 2, “stokes (Stokes) shifts” in the caption of Table 2, “Typy (Type) I photosensitizers” at the end of page 9, the misalignment of the fluorescence spectra and the photos in section 3 in the SI (pages S45-S52), inconsistence between the figure and caption of Figure S24 (compound 3r or 4b). Please carefully check.

Reviewer #2

(Remarks to the Author)
Chi and collaborators reported the Iminium-Assisted B(sp^2)-to-B(sp^3) transformation strategy for the enantioselective synthesis of tetracoordinate boron molecules. This represents an interesting transformation achieved through a simple reaction pattern, providing a straightforward method for the synthesis of chiral tetracoordinate boron molecules. However, there are some questions regarding the reaction mechanism that require clarification. Depending on the authors' responses,

the manuscript may potentially be recommended for acceptance.

（1）According to Table 1 (Condition Optimization), the authors identified the optimal conditions in Entry 15 and subsequently explored the substrate scope in Figure 2 based on these conditions. However, in the DFT calculation section, the roles of the co-catalyst and base were entirely omitted. This omission weakens the credibility of the mechanistic insights.

（2）The Lewis acid co-catalyst significantly improved the yield (Table 1), and the use of base additives (Entries 11–15) markedly altered the er value. Please provide a detailed explanation of these observations through DFT calculations, including the roles of the co-catalyst and base in the reaction mechanism.

（3）Influence of the Phenyl Group on Stereoselectivity:
The phenyl group (C) bonded to B in substrate 2 has a significant impact on stereoselectivity. For instance:

In compounds 4k, 4l, and 4n, the removal or alteration of the ortho-methyl substituents on the phenyl group leads to a decrease in the er value.

When C is replaced with an alkyl group (4p, 4q), the er value decreases further.

However, in the comparison of TS2_Re and TS2_Si in Figure S8, the C group does not appear to participate in the primary weak interactions. Please explain the underlying reasons for the influence of group C on stereoselectivity, as this aspect is not clearly addressed in the current manuscript.

The authors are encouraged to address these points to strengthen the mechanistic understanding of their work.

Reviewer #3

(Remarks to the Author)
This manuscript reports new synthetic methodology for the preparation of chiral compounds with a stereogenic boron atom. The condensation of salicylaldehyde derivatives with various BN heterocycles is catalysed by an amino thiourea to give a range of products is generally good yield with high enantioselectivity. The mechanism of the reaction is discussed in detail, supported by DFT calculations. The photophysical properties of some of the compounds are explored in-depth, alongside their synthetic utility and biological activity. The manuscript is well written, the supporting information detailed, and the products characterised to a high standard.

Overall, this is a nice piece of work that provides a new method to prepare this class of compounds. While the substrates are necessarily quite specific to allow the reaction to occur, the demonstration that this concept is viable to prepare stereogenic boron centres is significant. The paper also has lots of additional information of properties and applications, and will therefore have broad interest. I believe the manuscript is suitable for publication in Nat. Commun. after consideration of the following minor points.

1. Figure 1b) “tetracoordinate” in the heading is spelt incorrectly.
2. Page 6 – I would not describe the mechanism as a “dehydrative cycloaddition”, as this suggests a pericyclic nature. Maybe “dehydrative annulation” or simply “condensation” would be better.
3. Page 7, in the supporting information, intermediate I (formed from salicylaldehyde and the catalyst) is isolated and characterised. Was this ever used as a stoichiometric pre-catalyst to show that it can produce the observed product? If so, it would be useful to mention the result of this.
4. While the manuscript is generally well written and easy to follow, there are a few typographical and English language errors remaining. These should be picked-up during the editing process.

Reviewer #4

(Remarks to the Author)
The manuscript by Nong et al. describes an organocatalytic synthesis of chiral-at-boron compounds by addition of a nucleophile to a prochiral trivalent boron precursor. From a conceptual standpoint, there is significant originality in this research and I am enthusiastic about supporting its publication. Other asymmetric methods for the synthesis of these materials occur by reaction of prochiral four-coordinate boron compounds that contain two equivalent enantiotopic ligands. This paper represents the first strategy where a trivalent boron is the reaction precursor. Moreover, the catalysis is interesting and timely, and the research appears to be expertly conducted. I have a few minor concerns listed below, but a larger concern that gives me some pause, is that there doesn't yet seem to be a compelling use for these types of compounds in an enantiomerically enriched form. The applications described in the latter parts of the paper are interesting, but not truly convincing from a practical standpoint. Nonetheless, the fundamental science will be of interest to the readership and I am supportive of this report.

Comments:

1. Page 4, line 7: it is important to note that with strong bases the background process is "racemic" and results in lowering of

er. I would explicitly state this in the text.

2. Page 6, paragraph 5: the term "aza-Mannich" refers to a metalloenamine addition to an imine; this should be called "aminal formation"

3. According to the DFT study in Figure 4, the stereochemistry-determining step is reaction through TS2. Accordingly, it is necessary to calculate the conversion of the product of TS1–Si through TS2. TS2_Re and TS2_Si only originate from TS1_Re and thus the barrier for formation of the minor enantiomer hasn't been fully established.

4. It would be helpful if the authors could clearly explain the origin of enantioselectivity. The DFT results will give them a number, but readers will want to know what repulsive steric interaction penalizes the minor TS compared to the major, or what favorable attractive interaction is present in the major TS but absent in minor.

5. What interactions are present in bimolecular ensemble II (Figure 4)? Are the thiourea–amine hydrogen bonds already in place? If so (I suspect they are), it would be helpful to draw this explicitly.

6. Figure 5 seems somewhat redundant considering the detailed mechanism presentation in Figure 4.

7. While discussion of the optical properties of these molecules may have some interest, none of it seems to depend on the enantiomeric purity (other than the CD). I would recommend leaving all of this out of the paper and focus just on the synthetic aspects and the pesticide properties which are interesting and the latter shows configuration-dependent activity. In fact, it is quite interesting that in some cases the racemic compounds have lower activity than the less active antipode of the enantiomerically pure compound. Is there something more complex going on here the authors could expand on.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
All my concerns have been properly addressed, and publication is recommended.

Reviewer #2

(Remarks to the Author)
I have no further comments.

Reviewer #3

(Remarks to the Author)
This revised manuscript has carefully addressed the comments of the original reviewers, and the work has been improved by the revision process. The authors have added additional clarifications where needed and performed some additional experiments that add to their original findings.

Overall, this is an interesting article that provides details of a new synthetic method, mechanistic insight, alongside properties and applications. It will therefore be of broad interest and publication in Nat. Commun. is recommended.

Reviewer #4

(Remarks to the Author)
The authors have adequately addressed my concerns.

Reviewer #5

(Remarks to the Author)
The current manuscript described a synthetic method for the preparation of chiral organoboron compounds, with the anti-bacterial studies carried out to show the potential applications of the chiral products. As the authors claimed in their text, chiral organoboron compounds have not been studied in the field of pesticides development, which might be due to the challenges in their synthesis. It is therefore interesting to see the anti-bacterial activities of these unprecedented chiral structures. In contrast with most of the reports focusing on synthetic methods, the EC50 values of the chiral organoboron compounds have been examined and presented, which could reflect the bioactivities more clearly than the simple inhibition rates. In addition, the detailed experimental procedures and the full inhibition rates of all compounds have been correctly presented in the supplementary information. Overall, I consider this work an intriguing study that paved the new avenue towards the development of boron-containing chiral pesticides.
I did not find major technical or expressing errors in the bioactive evaluations. Some minor typos and suggestions are given below:

1. “We systematically.....of the compound 3 against Xoo and Xac (Table 3)”. It should be changed into “We systematically.....of the compounds 3 and 4 against.....”
2. The plants that could get infected by Xoo and Xac should be introduced, and the syndrome should be described, since most of the readers might not be familiar with these bacteria.

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Reviewer #1 has recommended acceptance of our manuscript after minor revisions.

a) Reviewer's comment: "*In Figure 6d, the curve labeled as 85% shows an unusual decrease in fluorescence intensity and retesting is recommended..*"

Our Response: We have re-evaluated the AIE (aggregation-induced emission) properties of the compound **3h**, and the updated data is now presented in the revised Figure 6d. Our results demonstrate that as the water content increased from 60% to 75%, the fluorescence intensity of the solution exhibited a significant enhancement accompanied by a redshift in the emission spectrum, which is consistent with the characteristic AIE effect. Subsequent increases in water content from 75% to 99% resulted in slight but gradual enhancements in fluorescence intensity.

b) Reviewer's comment: "*Calculations show that compounds **3a** and **3j** achieve intersystem crossing via the S1→T2 pathway. Is it possible to provide experimental characterizations to support the calculation results?*"

Our Response: We fully acknowledge the importance of experimental validation of these intersystem crossing processes. However, as far as we know, there are currently no established experimental techniques capable of directly probing the $S_1 \rightarrow T_2$ intersystem crossing pathway in these systems. This limitation is not unique to our study; computational approaches remain the primary tool for elucidating such ultrafast, nonradiative processes in molecular excited states. For instance, the works cited below, together with many others in this field, have relied on analogous theoretical frameworks to infer intersystem crossing mechanisms due to the inherent experimental challenges:

1. Hua, T., et al. Deep-blue organic light-emitting diodes for ultrahigh-definition displays. *Nature Photonics* **18**, 1161–1169 (2024).
2. Hu, Y., et al. Efficient selenium-integrated TADF OLEDs with reduced roll-off. *Nature Photonics* **16**, 803–810 (2022).
3. Cao, X., et al. Manipulating Exciton Dynamics toward Simultaneous High-Efficiency Narrowband Electroluminescence and Photon Upconversion by a Selenium-Incorporated Multiresonance Delayed Fluorescence Emitter. *J. Am. Chem. Soc.* **144**, 22976–22984 (2022).

c) Reviewer's comment: "*Figure 6a shows non-normalized absorption spectra, while it is described as normalized absorption spectra in the text.*"

Our Response: We apologize for the mistake. We have changed the description of Figure 6a from "normalized absorption spectra" into "absorption spectra" in the revised manuscript.

d) Reviewer's comment: "*The PLQY measurement has standard errors of <5%. Typically it is not necessary to keep decimals as the measurement cannot be so accurate (Table 2)*"

Our Response: We sincerely appreciate this insightful observation. As suggested, we have updated the PLQY values in Table 2 in the revised manuscript.

e) Reviewer's comment: "*The discussions on CD and CPL are too concise. More discussions are recommended, for example, by comparing with reported compounds and theoretical calculations.*"

Our Response: We have updated the discussion on page 9 of our revised manuscript as: "The chiroptical properties of the representative chiral-at-boron enantiomers were studied via circular dichroism (CD) and CPL spectroscopies (Fig. 6e, f and Figs S17-22). The CD and CPL spectra of the (*R*)-**3a** and (*S*)-**3a** in dichloromethane exhibit clear mirror images with distinct Cotton effects (Fig. 6e, f). Their luminescence dissymmetry factors (glum) were measured as $+5.3\times10^{-4}$ and -6.0×10^{-4}, respectively. Similarly, enantiomers **3k** and **4i** also display mirror-image CPL spectra in the 550–650 nm range, with closely matched glum values (Figs. S21-22). These glum values align with those of recently reported chiral tetracoordinate boron compounds exhibiting CPL activity.[3,7]"

f) Reviewer's comment: "*There are several typos and formatting mistakes, such as wrong title for Table 2, "stokes (Stokes) shifts" in the caption of Table 2, "Typy (Type) I photosensitizers" at the end of page 9, the misalignment of the fluorescence spectra and the photos in section 3 in the SI (pages S45-S52), inconsistence between the figure and caption of Figure S24 (compound **3r** or **4b**). Please carefully check.*"

Our Response: We sincerely apologize for these oversights. The following corrections have been implemented in the revised manuscript and SI:

The title of Table 2 has been updated.

We have changed the "stokes" into "Stokes" in Table 2.

"Type I photosensitizers" (corrected from "Typy I") has been revised on page 9.

Fluorescence spectra and images in Section 3 of the SI (pages S37–S57) have been realigned for consistency.

Figure S24 (Figure S25 in the the revised supplementary information) has been corrected to show compound **4b**, matching its caption.

Reviewer #2 has recommend publication of this paper after certain revisions on the reaction mechanism.

a) Reviewer's comment: "*According to Table 1 (Condition Optimization), the authors identified the optimal conditions in Entry 15 and subsequently explored the substrate scope in Figure 2 based on these conditions. However, in the DFT calculation section, the roles of the co-catalyst and base were entirely omitted. This omission weakens the credibility of the mechanistic insights.*"

Our Response: We respectfully disagree with the reviewer's comment on the credibility of the mechanistic insights. We would like to point out that even in the absence of the co-catalyst (AgOAc) and basic additives, as shown in Entry 8 of Table 1, a reasonably high enantioselectivity (er = 92 : 8) is already observed, compared to Entry 15 (er = 96 : 4). This difference in enantioselectivity translates to a Gibbs free energy difference of 0.4 kcal/mol at 25 ^{o} C, a value that is small and falls within the typical error margin of DFT methods. Therefore, it may be challenging to capture such a small barrier difference computationally. Thus, for our DFT studies, we have zoomed in on understanding the mechanistic pathways without the co-catalyst in the enantioselectivity step.

We considered the role of the co-catalyst in product release (see response in the next comment), where the possible role of co-catalyst AgOAc may be involved in the product **3a** release during the catalyst regeneration step VI⟶D (in Figure 4), rather than its role in enantioselectivity determination. We hope this clarifies the rationale behind our computational model.

b) Reviewer's comment: "*The Lewis acid co-catalyst significantly improved the yield (Table 1), and the use of base additives (Entries 11–15) markedly altered the er value. Please provide a detailed explanation of these observations through DFT calculations, including the roles of the co-catalyst and base in the reaction mechanism.*"

Our Response: We thank the reviewer for this suggestion.

As reviewer pointed out, the more prominent effect of the co-catalyst and base is reflected in the reaction yield (30% in Entry 8 *vs* 71% in Entry 15). To investigate this, we explored the role of AgOAc in facilitating product **3a** release in the catalyst regeneration step VI⟶D, Figure 4. Our results indicate that the AgOAc bound product **3a** lies at 1.9 kcal/mol below the starting reactants **D** and **1a**, thus, rendering the overall transformation is thermodynamically favorable. This suggests that the co-catalyst may play a key role in promoting product dissociation and catalyst turnover, rather than significantly influencing the enantioselectivity.

We have added the following discussion in the manuscript on page 7 to read:

"Finally, from **VI**, the release of product **3a**, along with the regeneration of the active catalyst **D** is facilitated by the co-catalyst AgOAc, which plays a key role in stabilizing the product **3a** complex, Figure 4. The AgOAc bound product **3a** lies at 1.9 kcal/mol below the starting reactants **D** and **1a**, thus, the overall transformation is thermodynamically favorable."

c) Reviewer's comment: "*Influence of the Phenyl Group on Stereoselectivity: The phenyl group (C) bonded to B in substrate **2** has a significant impact on stereoselectivity. For instance:*

*In compounds **4k**, **4l**, and **4n**, the removal or alteration of the ortho-methyl substituents on the phenyl group leads to a decrease in the er value.*

*When C is replaced with an alkyl group (**4p**, **4q**), the er value decreases further.*

*However, in the comparison of **TS2_Re** and **TS2_Si** in Figure S8, the C group does not appear to participate in the primary weak interactions. Please explain the underlying reasons for the influence of group C on stereoselectivity, as this aspect is not clearly addressed in the current manuscript.*"

Our Response: We acknowledge the variation in enantioselectivity observed across different substrates-e.g., **4k** (84:16), **4l** (85 : 15), **4n** (77 : 23), **4p** (71 : 29), and **4q** (65 : 35)-in comparison to substrate **2**, which exhibits an er of 96:4. These differences in enantioselectivity, compared to the model system, translate to Gibbs free energy differences of ~0.9-1.5 kcal/mol. We hypothesized that different substituents may have different non-covalent interactions in the competing TSs, compared to the prototypical system that we have studied, so that there will be difference in $\Delta\Delta G^{\ddagger}$ between the major and minor TSs. It is however, unfeasible, if not unreasonable, to study all substrates to ascertain the subtle influences of different substituents on the minute differences in enantioselectivity computationally.

Furthermore, our DFT investigation was designed to provide a detailed mechanistic understanding using substrate **2** (bearing a methyl substituent on the C ring) as a representative model. This approach is consistent with common practice in DFT mechanistic studies, which often focus on a single substrate to elucidate the reaction mechanism, rather than exhaustively modeling the entire substrate scope.

Finally, we clarify that the originally labelled **TS2_*Re*** and **TS2_*Si*** (which result both from **TS1_*Re*** earlier) control the stereoselectivity (E/Z selectivity) at the iminium carbon center, on the pathway leading to major enantiomer product **3a**. We have clearly mentioned these details in the main text on Page 6. However, to avoid any potential confusion, we have relabeled **TS2_*Re*** and **TS2_*Si*** as **TS2** and **TS2'**, respectively. Most importantly, our new calculations along the pathway originating from **TS1_*Si*** and leading to the minor product (**TS2_*minor*** and **TS2'_*minor***) reveal that, while **TS1** is the enantio-inducing transition state-favoring the formation of **3a** via **TS1_*Re*** over **TS1_*Si*** by 1.9 kcal mol^{-1}, the subsequent cyclization step (III → IV) via **TS2** is the overall enantio- and rate-determining step, since the competing reactivities of major vs minor pathways depend on their respective energetic spans. In this step, **TS2** is favored over **TS2_*minor*** by 2.8 kcal mol^{-1}, further supporting the kinetic preference for enantioselective formation of product **3a** (Please see our response to Reviewer 4, Comment 2 below).

Reviewer #3 has recommend publication of this paper after minor revisions.

a) Reviewer's comment: "*Figure 1b) "tetracoordinate" in the heading is spelt incorrectly.*"

Our Response: We have changed the "tetracordinate" into "tetracoordinate" in the Figure 1b) of the revised manuscript.

b) Reviewer's comment: "*Page 6 - I would not describe the mechanism as a "dehydrative cycloaddition", as this suggests a pericyclic nature. Maybe "dehydrative annulation" or simply "condensation" would be better.*"

Our Response: We have changed the description of the mechanism from "dehydrative cycloaddition" into "dehydrative annulation" on page 6.

c) Reviewer's comment: "*Page 7, in the supporting information, intermediate **I** (formed from salicylaldehyde and the catalyst) is isolated and characterised. Was this ever used as a stoichiometric pre-catalyst to show that it can produce the observed product? If so, it would be useful to mention the result of this.*"

Our Response: We used intermediate **I** as a stoichiometric pre-catalyst to catalysis the reaction between the salicylaldehyde **1a** and the BN phenanthrene **2a**. The target product **3a** could be afforded in 63% yield and 97:3 er value. We have added the obtained experimental results on Page S16 of the revised supplementary information.

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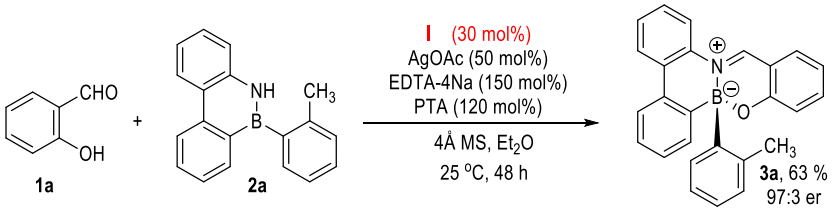

Figure R1. Construction of chiral B(sp^3) center via pre-catalyst intermediate **I**.

d) Reviewer's comment: "*While the manuscript is generally well written and easy to follow, there are a few typographical and English language errors remaining. These should be picked-up during the editing process*"

Our Response: We sincerely thank the reviewer for the valuable suggestion. We carefully examined the typographical and English language errors and have thoroughly corrected them in the revised manuscript.

Reviewer #4 has recommend publication of this paper after minor revisions.

a) Reviewer's comment: "*Page 4, line 7: it is important to note that with strong bases the background process is "racemic" and results inlowering of er. I would explicitly state this in the text.*"

Our Response: We have added a description that strong base could lead to racemization during the catalytic process on page 4 of the revised manuscript:

"……Basic additives were found effective in promoting the reaction yields (e.g., Entries 11 to 13). The use of the strong basic additives could increase the yield of the target product 3a, but with sacrifice of the enantioselectivity……. ."

b) Reviewer's comment: *Page 6, paragraph 5: the term "aza-Mannich" refers to a metalloenamine addition to an imine; this should be called "aminal formation*".

Our Response: We have revised the text accordingly on Page 6.

c) Reviewer's comment: "*According to the DFT study in Figure 4, the stereochemistry-determining step is reaction through **TS2**. Accordingly, it is necessary to calculate the conversion of the product of **TS1_Si** through **TS2. TS2_Re** and T**S2_Si** only originate from **TS1_Re** and thus the barrier for formation of the minor enantiomer hasn't been fully established.*"

Our Response: We thank the reviewer for this suggestion.

As suggested, we located the relevant transition states (**TS2_*minor*** and **TS2'_*minor***) along the pathway originating from **TS1_*Si*** and leading to the minor enantiomer, since the competing reactivities of major vs minor pathways depend on their respective energetic spans. Our new results indicate that the stereoselective cyclization step (**III** → **IV**) is both enantio- and rate-determining, with **TS2_*minor*** lying 2.8 kcal mol^{-1} higher in free energy than **TS2**, consistent with the preferential formation of enantio-selective product **3a**. Note that in our previous version, **TS2_*Re*** and **TS2_*Si*** (which result both from **TS1_*Re*** earlier) control the stereoselectivity (E/Z selectivity) at the iminium carbon center.

We have updated Figure 4 accordingly and added arrows to highlight the enantio-determining transition states (**TS2** and **TS2_*minor***) and the corresponding $\Delta\Delta G^{\ddagger}$, thereby making the selectivity origin more explicit.

We have revised Figure 4 in the main text accordingly:

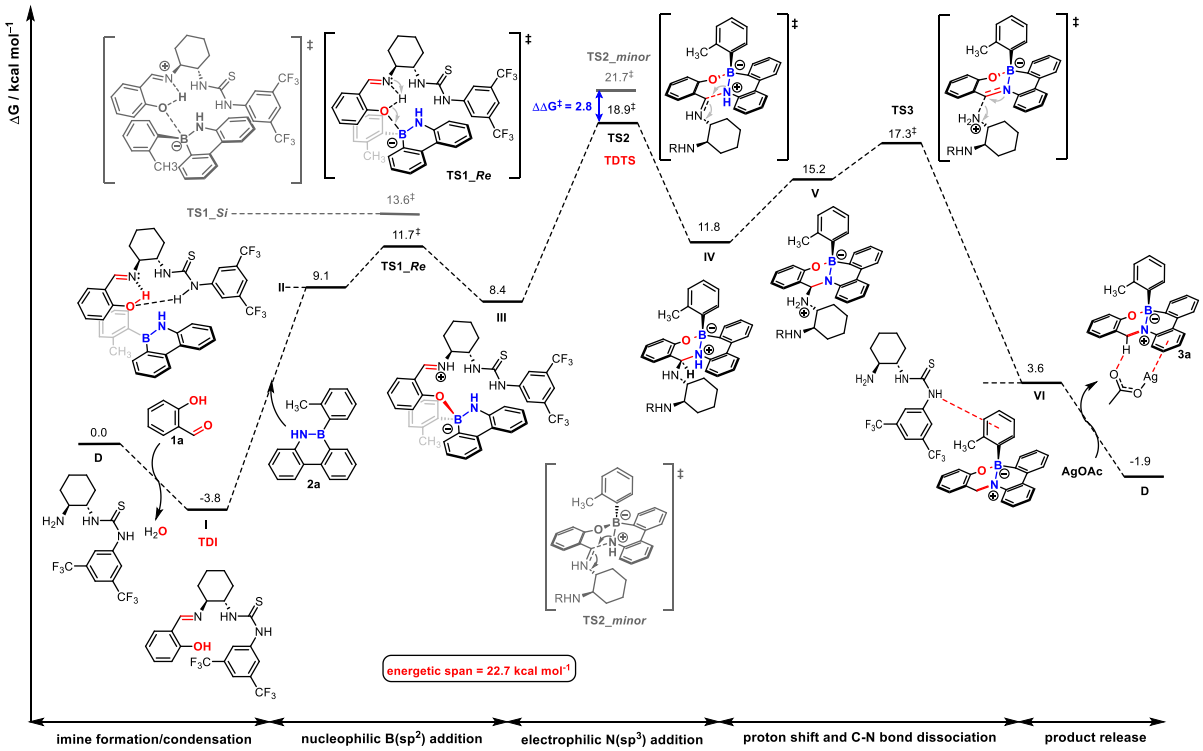

Figure R2. Gibbs free energy profile for the enantioselective formation of chiral B(sp³) compound 3a. The free energies were computed at SMD(diethylether)-M06-2X/def2-TZVP//M06-2X/(def2-TZVPPD for Ag and def2-SVP for all other atoms) level of theory. All values are given in kcal mol^{-1} with respect to the starting catalyst **D**, and all other substrates. TDI, turnover frequency-determining intermediate; TDTS, turnover frequency-determining transition state.

We have added the following discussion on the enantio-determining TS structures in the manuscript to read:

"It is worth noting that along the pathway originating from **TS1_*Si*** and leading to the minor product, the lowest-energy cyclization transition state **TS2_*minor*** lies 2.8 kcal mol^{-1} higher in free energy than **TS2**, which leads to the major enantio-selective product **3a**, Fig. 4 (see Fig. S8 for the DFT optimized structures). Notably, this **III** → **IV** cyclization step via **TS2** constitutes the overall enantio-determining and irreversible step, as the forward transformation from **IV** to **3a** via **TS3** proceeds with a lower barrier (5.5 kcal mol^{-1}) than the reverse reaction from **IV** to **III** via **TS2** (barrier of 7.1 kcal mol^{-1}), further reinforcing the kinetic preference for the formation of enantio-selective product **3a**, Fig. 4."

and the discussion in Section 3.6 in the supporting information to read:

3.6 Enantio-determining intramolecular aminal formation step via stereoselective ring closure

"……Alternatively, along the pathway originating from **TS1_*Si*** and leading to the minor product, the corresponding **TS2** structures (**TS2_*minor*** and **TS2'_*minor***) reveal that the lowest energy **TS2_*minor*** (21.7 kcal mol^{-1}) lies 2.8 kcal mol^{-1} higher than the corresponding **TS2** (18.9 kcal mol^{-1}) leading to the major product **3a**, Figure S8. While **TS1** serves as the enantio-inducing transition state, favoring the pathway leading to **3a** via **TS1_*Re*** over **TS1_*Si*** by 1.9 kcal mol^{-1}, the subsequent cyclization step (**III** → **IV**) via **TS2** is the enantio-determining step, with **TS2** favored over **TS2_*minor*** by 2.8 kcal mol^{-1}, thereby reinforcing the kinetic preference for enantioselective formation of product **3a**……."

d) Reviewer's comment: "*It would be helpful if the authors could clearly explain the origin of enantioselectivity. The DFT results will give them a number, but readers will want to know what repulsive steric interaction penalizes the minor TS compared to the major, or what favorable attractive interaction is present in the major TS but absent in minor.*"

Our Response: We thank the reviewer for this suggestion.

We discussed the enhanced stability of key TSs **TS1_*Re*** and **TS2** arising from favorable non-covalent interactions, such as π–π stacking and C–H…π interactions based on geometry and NCI plot analysis (Figure S7, S8, and S10). To further understand the origin of enantioselectivity, we carried out the distortion-interaction analysis on these key TSs (**TS1_*Re*** and **TS2**) and the corresponding less stable isomers (**TS1_*Si*** and **TS2_*minor***), providing deeper insight into the energetic factors governing B–O bond formation and the stereoselective cyclization step. The analysis reveals that the preference for **TS1_*Re*** over **TS1_*Si*** is primarily driven by its lower distortion energy, which offsets its less favorable interaction energy. Similarly, **TS2** is favored over **TS2_*minor*** due to significantly more stabilizing interaction energy, leading to a lower overall activation barrier and supporting the enantio-selective formation of **3a**.

We have added the following discussion on the enantio-determining TS structures in the manuscript to read:

"**TS2** is favored over **TS2_*minor*** potentially due to more favorable non-covalent interactions, such as π–π stacking and C–H…π interactions (Fig. S10), along with more stabilizing interaction energy between the two fragments constituting the transition state (Table S6)."

and added a new Section 3.7 in the supporting information:

3.7 Distortion-interaction Analysis for enantio-inducing and enantio-determining TSs

Distortion-interaction analysis is applied to key TSs (**TS1** and **TS2**) to discern the factors affecting enantioselectivity. The transition state structures are decomposed by dividing the chiral imine intermediate **I**, and boron substrate **2a** as components. Single point calculations with SMD(diethylether) solvent correction were applied performed at M06-2X/def2-TZVP level of theory to obtain distortion and interaction energies. The distortion energy is given by:

$$E_{dist} = E_{TS,frag1} + E_{TS,frag2} - (E_{eq,frag1} + E_{eq,frag2})$$

where *TS,frag1,2* represent individual fragments in their distorted transition state geometries; and *eq,frag1,2* represent individual fragments in their optimized, equilibrium ground-state geometries; the interaction energy is given by:

$$E_{int} = E_{TS} - (E_{TS,frag1} + E_{TS,frag2})$$

which accounts for the stabilizing interactions (e.g., electrostatic, orbital, dispersion) between the distorted fragments in the TS.

Thus, the total activation energy is given by:

$$\Delta E^{\ddagger} = E_{dist} + E_{int}.$$

Note that this single point activation energy and the activation energy differences ΔΔE‡ between the TSs (**TS1_*Re*** vs. **TS1_*Si***, and **TS2** vs. **TS2_*minor***) may be different from the Gibbs energy differences ΔΔG‡ that is computed fully (including vibrational frequencies analysis) at SMD(diethylether)-M06-2X/def2-TZVP//M06-2X/def2-SVP level of theory.

This analysis gives a ΔΔ$E^{\ddagger}$ **(TS1)** of 1.1 kcal mol^{-1} in favor of **TS1_*Re*** over **TS1_*Si***. Although **TS1_*Re*** exhibits a lower interaction energy **(E_{int})** by 1.5 kcal mol^{-1}, this is outweighed by its distortion energy **(E_{dist})**, which is 2.6 kcal mol^{-1} lower than **TS1_*Si***, Table S6. Similarly, the ΔΔE‡ **(TS)** is 3.3 kcal mol^{-1} in favor of **TS2** relative to **TS2_*minor***, primarily due to a significantly more stabilizing **E_{int}** (–67.1 kcal mol^{-1} for **TS2** vs. –57.6 kcal mol^{-1} for **TS2_*minor***). While **TS2** displays a slightly higher **E_{dist}** (73.0 kcal mol^{-1} vs. 66.8 kcal mol^{-1}), this is more than compensated by its favorable interaction energy, resulting in a lower overall ΔE‡ (5.9 kcal mol^{-1} vs. 9.2 kcal mol^{-1}) and making **TS2** the more favorable transition state, Table S6.

Table R1. Distortion-interaction analysis

Transition State	$\Delta E^{\ddagger}$	E_{dist}	E_{int}
TS1_*Re*	0.7	13.6	-12.9
TS1_*Si*	1.8	16.2	-14.4
TS2	5.9	73.0	-67.1
TS2_*minor*	9.2	66.8	-57.6

e) Reviewer's comment: "*What interactions are present in bimolecular ensemble **II** (Figure 4)? Are the thiourea–amine hydrogen bonds already in place? If so (I suspect they are), it would be helpful to draw this explicitly.*"

Our Response: We revised the intermediate **II** structure in Figure 4.

f) Reviewer's comment: "Figure 5 seems somewhat redundant considering the detailed mechanism presentation in Figure 4."

Our Response: We thank this reviewer for the valuable suggestion and agree with him that the mechanism has been detailed in Figure 4. However, we would like to keep the Figure 5 since it is concise and much easier for readers to follow than Figure 4 to get an overall picture on the reaction mechanism. It could be regarded as the conclusion on the mechanistic investigation.

g) Reviewer's comment: "*While discussion of the optical properties of these molecules may have some interest, none of it seems to depend on the enantiomeric purity (other than the CD). I would recommend leaving all of this out of the paper and focus just on the synthetic aspects and the pesticide properties which are interesting and the latter shows configurationdependent activity. In fact, it is quite interesting that in some cases the racemic compounds have lower activity than the less active antipode of the enantiomerically pure compound. Is there something more complex going on here the authors could expand on.*"

Our Response: We thank this reviewer for the valuable suggestion and fully agree with him that most of the optical properties of the tetra-coordinated boron products we obtained did not rely on the enantiomeric purity. However, we have to choose to keep this section since the products we obtained are close analogs to the BOSPY that has been extensively studied in the development of novel optical materials. Providing the optical properties of these new chiral structures would be significant to the scientists focusing on the optical material development, which would greatly help broaden the scope of readers who would be interested in this study.

We are currently systematically studying the anti-bacterial activities of the products we obtained for plant protection. The relationship between the chiral configurations and the pesticide bioactivities has provided interesting information on the anti-bacterial mechanistic investigations. This study will be published as a separated work in due course.

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September 22, 2025

(Manuscript No.: NCOMMS-25-06493-T)

Reviewer #1 has recommended acceptance of our manuscript.

Reviewer #2 has recommended acceptance of our manuscript.

Reviewer #3 has recommended acceptance of our manuscript.

Reviewer #4 has recommended acceptance of our manuscript.

Reviewer #5 has recommended acceptance of our manuscript after minor revisions.

a) Reviewer's comment: "We systematically.....of the compound **3** against *Xoo* and *Xac* (Table 3)." It should be changed into "We systematically.....of the compounds **3** and **4** against....."

Our Response: We have changed the "We systematically.....of the compound 3 against Xoo and Xac (Table 3)." into "We systematically.....of the compounds 3 and 4 against....." on Page 11 of the revised manuscript.

b) Reviewer's comment: The plants that could get infected by *Xoo* and *Xac* should be introduced, and the syndrome should be described, since most of the readers might not be familiar with these bacteria.

Our Response: We have added the relevant expressions on Page 11 of the revised manuscript.