nature portfolio

Peer Review File

Palladium-Catalyzed Enantioselective β-Hydride Elimination for the Construction of Remote Stereocenters

Corresponding Author: Professor Weiwei Zi

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 Zi and colleagues reports a palladium-catalyzed enantioselective β-hydride elimination reaction which is a seldom studied area. By using 1-vinylcyclohexyl acetates as the substrate, this transformation provides a rapid access to enantioenriched cyclohexenes featuring a C4-remote stereocenter. Such structural motifs are highly valuable and commonly found in bioactive molecules. Previous studies on enantioselective β-hydride elimination have mainly focused on creating axial chirality; this work represents a breakthrough that targets the construction of central chirality. The manuscript includes all the essential elements expected in a paper on asymmetric catalysis for publication in Nature Communications, such as a wide substrate scope, useful synthetic applications, detailed mechanism studies, and a well-prepared supporting information file. In my viewpoint, this is a nice reaction methodology and I fully support its publication in Nature Communications.

Some concerns that might be addressed during the revisions are as follows:

1. The scope of the 1-vinylcyclohexyl acetate substrate is quite comprehensive. However, the reviewer wonders whether 1-vinylcyclobutyl acetate is a suitable substrate for this enantioselective β-hydride elimination reaction? This substrate can yield chiral cyclobutene, which is another valuable framework in organic synthesis.

2. Why did the author choose different reaction conditions for the kinetic experiments (0.375 mol% Pd2dba3, 0.9 mol% L11, 32 °C) compared to the standard conditions (0.75 mol% Pd2(dba)3, 1.8 mol% L11, 50 °C)?

3. Some terms or symbols should be explained in the main text or footnote, such as “nd”, “w/o” and “MTBE” in Table 1. In addition, the structure of L3 in Table 1 should be redrawn.

Reviewer #2

(Remarks to the Author)
Transition-metal-catalyzed β-hydride elimination converts a Csp3-Csp3 bond into an olefin without producing any direct stereoelements. While early transformations have successfully achieved axial chirality construction, preparing a central chirality through β-hydride elimination remains unresolved. In this manuscript, Zi and Sun present a novel palladium-catalyzed enantioselective desymmetric β-hydride elimination reaction, specifically designed to construct cyclohexenes featuring C4-remote stereocenters. The authors successfully synthesized a series of 1,3-dienes with a chiral center at the C4 position, utilizing 1-vinylcyclohexyl acetates as starting materials. This well-crafted transformation not only showcases the authors' innovative approach but also provides a valuable synthetic framework for further applications. The significance of the resulting products is underscored by their application in the total synthesis of biologically active compounds, such as (-)-oleuropein and (-)-7-hydroxyterpineol, demonstrating the practical utility of this methodology in complex organic synthesis. Moreover, the authors thoroughly investigate the reaction mechanism, confirming their findings through a combination of computational studies and experimental data. Their results reveal that the β-H elimination step is both the rate-limiting and enantioselectivity-determining step of the reaction, providing crucial insights into the factors influencing the stereochemical outcomes. I enjoy this work so much that I support its acceptance in Nature Communications, provided the following issues are addressed.

1. What would occur if an internal alkene were used instead of a terminal alkene in the reaction?
2. Using a four-membered starting material, is it feasible to employ a similar transformation to synthesize the corresponding cyclobutene that contains a C3 stereocenter?
3. As illustrated in Table 1, dioxane demonstrates significantly better enantiocontrol compared to THF. What are the main factors contributing to this difference? Additionally, why does the use of UBU as a base result in a substantial decrease in enantioselectivity?
4. Some typos:
On page 2, line 23, "Jacoben" should be "Jacobsen".
On page 7, line 17, "serve as useful synthon" should be revised as "serve as a useful synthon".
On page 10, line 2, "Caculation method" should be "Calculation method".
On page 12, line 3, "Studies the Non-covalent interactions" should be revised as "Studies of the Non-covalent interactions".
On page 14, line 10 and line 25, the abbreviation "Nat. Syn." needs to be revised as "Nat. Synth."

Reviewer #3

(Remarks to the Author)
Zi and colleagues submitted a manuscript describing their development of a palladium-catalyzed method for the construction of chiral carbons via a b-H elimination step, leading to the synthesis of substituted chiral cyclohexene compounds. First, the authors performed a series of detailed condition optimizations, ultimately identifying the Trost ligand as the optimal ligand. They then demonstrated the reaction's scope by synthesizing 31 substituted chiral cyclohexene compounds. Subsequently, some product applications and mechanistic studies were conducted, and a reliable reaction mechanism was proposed based on DFT calculations.

From the perspective of product application, this work provides a rapid and efficient method for synthesizing substituted chiral cyclohexenes, offering a valuable tool and insights for pharmaceutical synthesis. From a synthetic methodology standpoint, the study employs a straightforward oxidative addition/b-H elimination process to construct useful substrates. However, the methodological innovation is relatively limited. Regarding substrate scope, the authors demonstrated over 30 examples, including some with notable functional groups. Nevertheless, the range of applicable substrate frameworks is narrow, being limited to 1-vinylcyclohexyl acetate derivatives. The work excels in product applications and mechanistic studies.

In summary, this study presents a practical approach for constructing substituted chiral cyclohexene building blocks. However, the level of innovation is relatively modest. Additionally, considering the issues outlined below, we believe that the manuscript requires substantial improvement and supplementation. Once revised and enhanced, the manuscript may be suitable for publication in Nature Communications.

The manuscript includes, but is not limited to, the following issues, which we propose for the authors' reference and revision:

1. In the IGMH analysis, van der Waals interactions are reported between the aromatic rings of the substrate and ligand. However, not all substrates contain aromatic rings (e.g., 2n-2r), and there is no significant improvement in yield or enantioselectivity for substrates with aromatic rings compared to those without. Please clarify the role and magnitude of the van der Waals interactions in the reaction.

2. Can the enantiomeric excess (ee) values of products 2y and 4e be measured? If so, please include them; if not, provide a rationale. Additionally, please measure and report the ee values of products 10 and 11 to demonstrate that the synthetic process does not lead to racemization.

3. Are substrates with frameworks such as (E)-4-phenyl-1-(prop-1-en-1-yl)cyclohexyl acetate, (E)-4-phenyl-1-styrylcyclohexyl acetate, 3-phenyl-1-vinylcyclopentyl acetate, or 4-phenyl-1-vinylcycloheptyl acetate compatible with the reaction system? If possible, please evaluate their compatibility.

4. To aid reproducibility, we recommend providing approximate TLC Rf values for each synthesized compound in the Supporting Information (SI).

5. We understand that finding suitable HPLC conditions for chiral resolution can be challenging. However, we strongly recommend further optimizing the HPLC conditions to accurately determine the ee values of the products, including but not limited to products 2b, 2e, etc. The current HPLC resolution for these products appears insufficient, potentially leading to deviations in the reported ee values. Additionally, please confirm the resolution conditions for products 2k and 2m, as the retention times of the racemic and chiral products differ significantly.

We hope these suggestions help improve the manuscript's clarity and scientific rigor.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have completely addreesed my concerns in the prior review and I believe it is now suitable for publication.

Reviewer #2

(Remarks to the Author)
The authors have addressed most of the points raised. I would like to recommend the publication of this manuscript in Nature Communications in current version.

Reviewer #3

(Remarks to the Author)
Since the authors have carefully addressed the issues of concern, including interpretation of substrate-ligand interactions, optimization of ee value measurement, further demonstration of substrate compatibility, and determination of the absolute configuration of the product, we have no additional comments on this manuscript and recommend its acceptance.

Reviewer #1

This manuscript by Zi and colleagues reports a palladium-catalyzed enantioselective β-hydride elimination reaction which is a seldom studied area. By using 1-vinylcyclohexyl acetates as the substrate, this transformation provides a rapid access to enantioenriched cyclohexenes featuring a C4-remote stereocenter. Such structural motifs are highly valuable and commonly found in bioactive molecules. Previous studies on enantioselective β-hydride elimination have mainly focused on creating axial chirality; this work represents a breakthrough that targets the construction of central chirality. The manuscript includes all the essential elements expected in a paper on asymmetric catalysis for publication in Nature Communications, such as a wide substrate scope, useful synthetic applications, detailed mechanism studies, and a well-prepared supporting information file. In my viewpoint, this is a nice reaction methodology and I fully support its publication in Nature Communications.

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A1. We have performed some preliminary investigations of the reaction for 1-vinylcyclobutyl acetate. The reaction occurred but the corresponding product is quite unstable, and could not be isolated.

Q2. Why did the author choose different reaction conditions for the kinetic experiments (0.375 mol% Pd2dba3, 0.9 mol% L11, 32 °C) compared to the standard conditions (0.75 mol% Pd2(dba)3, 1.8 mol% L11, 50 °C)?
A2. When using standard reaction conditions, we found that the initial reaction rate was very fast and very difficult to determine accurately. Therefore, we appropriately reduced the reaction concentration and temperature in order to obtain the initial reaction rate more accurately and facilitate the determination of the KIE value.

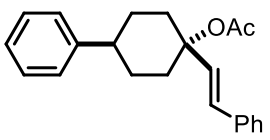
Q3. Some terms or symbols should be explained in the main text or footnote, such as “nd”, “w/o” and “MTBE” in Table 1. In addition, the structure of L3 in Table 1 should be redrawn.
A3. All these issues have been addressed in the revised manuscript.

Response: We thank the reviewer for these kind comments and valuable suggestions.

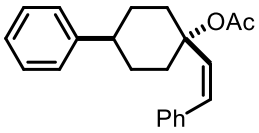
Reviewer #2

Transition-metal-catalyzed β-hydride elimination converts a Csp3-Csp3 bond into an olefin without producing any direct stereoelements. While early transformations have successfully achieved axial chirality construction, preparing a central chirality through β-hydride elimination remains unresolved. In this manuscript, Zi and Sun present a novel palladium-catalyzed enantioselective desymmetric β-hydride elimination reaction, specifically designed to construct cyclohexenes featuring C4-remote stereocenters. The authors successfully synthesized a series of 1,3-dienes with a chiral center at the C4 position, utilizing 1-vinylcyclohexyl acetates as starting materials. This well-crafted transformation not only showcases the authors' innovative approach but also provides a valuable synthetic framework for further applications. The significance of the resulting products is underscored by their application in the total synthesis of biologically active compounds, such as (-)-oleuropein and (-)-7-hydroxyterpineol, demonstrating the practical utility of this methodology in complex organic synthesis. Moreover, the authors thoroughly investigate the reaction mechanism, confirming their findings through a combination of computational studies and experimental data. Their results reveal that the β-H elimination step is both the rate-limiting and enantioselectivity-determining step of the reaction, providing crucial insights into the factors influencing the stereochemical outcomes. I enjoy this work so much that I support its acceptance in Nature Communications, provided the following issues are addressed.

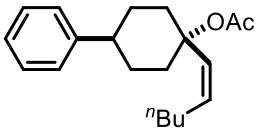
Q1. What would occur if an internal alkene were used instead of a terminal alkene in the reaction?
A1. We have prepared some substrates with an internal alkenes (shown below). Unfortunately, these substrates are inert under standard conditions. The procedure of preparing these substrates and the reaction outcome are enclosed in the supplementary files.



S6a



S6b



S6c

Q2. Using a four-membered starting material, is it feasible to employ a similar transformation to synthesize the corresponding cyclobutene that contains a C3 stereocenter?
A2. We have performed some preliminary investigations of the reaction for 1-vinylcyclobutyl acetate. The reaction occurred but the corresponding product is quite unstable, and could not be isolated.

Q3. As illustrated in Table 1, dioxane demonstrates significantly better enantiocontrol compared to THF. What are the main factors contributing to this difference? Additionally, why does the use of UBU as a base result in a substantial decrease in enantioselectivity?
A3. Solvent effect is important in transition metal catalysis. Probably due the weak coordination property of ether to the Pd, ether solvent gave better results in our system. But so far we have no idea why dioxane give improved ee values comparing to THF.
When DBU is used as the base, the base mediated background elimination reaction would occur (without the involving of Pd), resulting the decreasing of ee values.

Q4. Some typos:

On page 2, line 23, "Jacoben" should be "Jacobsen".

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A4. These typos have been revised accordingly.

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Reviewer #3

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A1. During the IGMH analysis, we did not observe any dominated arene-specific interactions, such as C-H…π or π…π stacking, between the aromatic rings of the substrate and the ligand in transition state **E**. In the subsequent energy decomposition analysis, we found that electrostatics and induction were the major contributors to the lower energy of transition state **E** compared to transition state **E′** . Since these interactions are not specific to the benzene ring, good enantioselectivity can still be observed for other products that are not substituted with an aryl group.

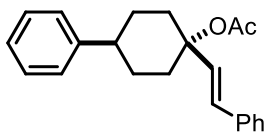
Q2. Can the enantiomeric excess (ee) values of products 2y and 4e be measured? If so, please include them; if not, provide a rationale. Additionally, please measure and report the ee values of products 10 and 11 to demonstrate that the synthetic process does not lead to racemization.

A2. We use an enantiopure substrate, where the amino acid moiety has a 100% S configuration. As

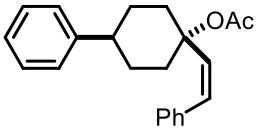
a result, the stereocontrol of the β-elimination reaction (for **2y**) is reflected in the diastereomeric ratio (dr) value. For compounds **4e**, the diastereomeric mixtures (dr = 1.3:1) could not be isolated through column purification. We attempted to analyze the mixture of compounds **4e** using chiral HPLC but were unable to identify suitable conditions to resolve all four peaks. Since the C4 stereocenter does not participate in the Diels-Alder reaction, we believe its stereochemistry is likely well-maintained. For products **10** and **11**, the ee value of **6** was measured, and the C4 stereocenter was not involved in the following transformations, which would not lead to racemization. Besides, products **10** and **11** are known compounds. We measured the specific rotations of products **10** and **11**, and the results were consistent with those reported in the literature. (Ref. for **10**: https://doi.org/10.1248/cpb.53.783, for **11**: https://doi.org/10.1002/jps.2600700417.)

Q3. Are substrates with frameworks such as (E)-4-phenyl-1-(prop-1-en-1-yl)cyclohexyl acetate, (E)-4-phenyl-1-styrylcyclohexyl acetate, 3-phenyl-1-vinylcyclopentyl acetate, or 4-phenyl-1-vinylcycloheptyl acetate compatible with the reaction system? If possible, please evaluate their compatibility.

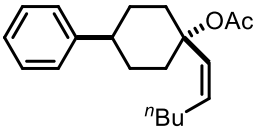
A3. We have prepared several substrates containing internal alkenes (shown below). Unfortunately, these substrates are inert under standard conditions. The procedures for preparing these substrates and the reaction outcomes are included in the supplementary files.



S6a

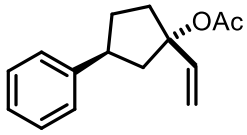


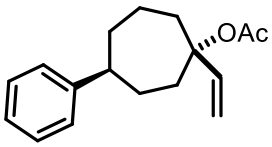
S6b



S6c

We did not conduct the reaction investigation of 3-phenyl-1-vinylcyclopentyl acetate and 4-phenyl-1-vinylcycloheptyl acetate because these substrates are not C2-symmetric and contain an intrinsic chiral center. The stereochemistry of these substrates would be complicated because of simultaneous substrate stereo-induction and catalyst stereocontrol.



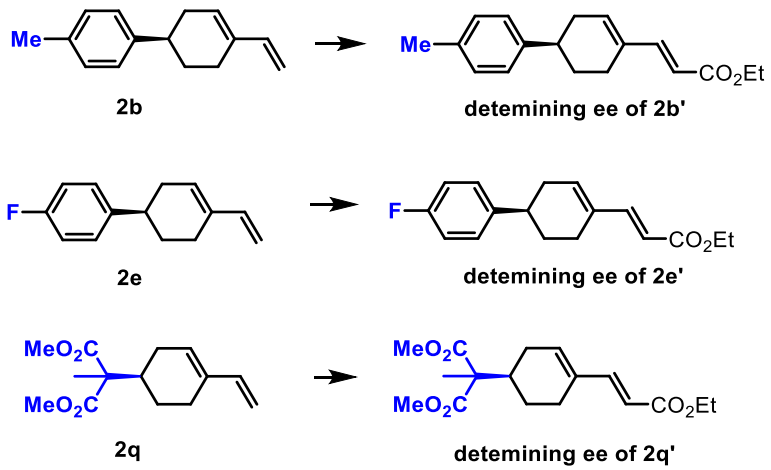


Q4. To aid reproducibility, we recommend providing approximate TLC Rf values for each synthesized compound in the Supporting Information (SI).

A4. The Rf values for all synthesized compounds were added in the SI.

Q5. We understand that finding suitable HPLC conditions for chiral resolution can be challenging. However, we strongly recommend further optimizing the HPLC conditions to accurately determine the ee values of the products, including but not limited to products 2b, 2e, etc. The current HPLC resolution for these products appears insufficient, potentially leading to deviations in the reported ee values. Additionally, please confirm the resolution conditions for products 2k and 2m, as the retention times of the racemic and chiral products differ significantly.

A5. The polarity of the products are very small, making it difficult to find suitable chiral HPLC resolution conditions. We have revised HPLC spectrums for 2k and 2m. Regarding to 2b, 2e, and 2q, we failed to found good HPLC conditions for them. Therefore 2b, 2e, and 2q were transformed to **2b′** , **2e′** and **2q′** , respectively, to determine the ee values. The identification of **2b′** , **2e′** and **2q′** **,** includind the HPLC spetrums are enclosed in the revised SI file.



Response: We thank the reviewer for these kind comments and valuable suggestions.