nature portfolio

Peer Review File

Switchable annulation paths to diverse N-bridged bicyclic scaffolds via ligand-directed dicarbonylation

Corresponding Author: Professor Xiao-Feng Wu

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)
Recommendation: The proposed work could be considered for publication in Nature Communications after major revision.

General Comment: In this manuscript, X.-F. Wu and co-workers report a novel divergent palladium-catalyzed carbonylation strategy for the synthesis of less common bicyclic nitrogen-containing heterocycles, enabled by the judicious choice of phosphorus ligands. The methodology exhibits a broad substrate scope and good tolerance toward a wide range of functional groups. Additional value is provided by the successful functionalization and derivatization of pharmaceutically relevant and naturally occurring compounds.
Mechanistic insight is supported by well-designed control experiments, which suggest the involvement of a common key intermediate that can be selectively converted into the desired products under standard reaction conditions. Moreover, deuterium-labeling experiments further corroborate the proposed reaction mechanism. Overall, the manuscript is clearly written, and in most cases the experimental data are reported in an appropriate and rigorous manner.
Taken together, this study represents a valuable contribution to the field of palladium-catalyzed carbonylation chemistry and will be of broad interest to the scientific community. For these reasons, I recommend publication in Nature Communications after major revision. Detailed comments are provided below.

Additional Comments:
• To provide a more comprehensive overview of the state of the art, the authors are encouraged to cite relevant literature in the main text, including:
Schiroli et al. (doi: 10.1002/adsc.202401183), describing a palladium-catalyzed carbonylative approach to nitrogen heterocycles with further derivatization toward peptide synthesis.
Pancrazzi et al.(Org. Lett. 2020, 10.1021/acs.orglett.0c00171), reporting a double cyclization strategy in carbonylation reactions to enhance molecular complexity.
• In the Supporting Information, the resolution of several molecular structure figures is poor and should be improved.
• The 1H and 13C-NMR spectra of compound 3c appear to be inverted.
• The purity of compounds 3f, 3u (notably in the 1.5–1.0 ppm region), 3ab, and 3ak could be improved.
• In several NMR spectra, proton integrations are reported twice in the spectra, and integrations are also included in the 13C-NMR spectra. Please clarify whether there is a specific reason for this representation.

Reviewer #2

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature

Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #3

(Remarks to the Author)
The manuscript describes a palladium-catalyzed, ligand-directed dicarbonylation of cyclobutenols, CO, and amines to afford 3-azabicyclo[3.2.0]heptane and 3-azabicyclo[3.1.1]heptane scaffolds in low to moderate yields. This reaction was similar to the authors' previous work on palladium-catalyzed aminocarbonylation of vinylcyclobutanols for the synthesis of α-substituted β,γ-unsaturated cyclobutanecarboxamides (Org. Lett. 2025, 27, 11644). The current study only extends their previous work by replacing vinylcyclobutanol with cyclobutanol to produce β,γ-unsaturated cyclobutanecarboxamide, which further undergoes intramolecular palladium-catalyzed hydroamidocarbonylation. In fact, the similar intramolecular palladium-catalyzed hydroamidocarbonylation procedure has also been reported by Dong and coworkers (Angew. Chem. Int. Ed. 2024, 63, e202410967; J. Org. Chem. 2023, 88, 5036), although the authors did not cite these two references. The proposed catalytic cycle is not substantiated by experimental or computational evidence that distinguishes it from the mechanism already outlined in their earlier cyclobutanol work. The key question such as how the ligand structure controls the regioselectivity is not addressed beyond empirical observation. This manuscript just applies an analogous mechanism (Pd-hydride formation, alkene insertion, CO migration, and nucleophilic attack by an amine) to a similar substrate class, without introducing a new activation mode, a novel ligand design, or a stereocontrol strategy.
Therefore, this manuscript lacks novelty and does not provide the depth of mechanistic insights required for a high-level journal. It does not belong in the Nature Communications.

Reviewer #4

(Remarks to the Author)
Wu and co-workers report on the synthesis of distinct N-bridged heterobicycles via Pd-catalysed dicarbonylation processes from a strained four membered ring substrate.
The manuscript is very interesting, and the study is well performed and includes a mechanistic investigation explaining the formation of both types of products. The scope of substrate used in large and moderate to high yields were obtained in most cases.
The authors also demonstrate the potential of these systems to access biomolecule scaffolds of interest and using a model substrate, they show the derivatives that can be obtained from the dicarbonyl products formed during catalysis.
The paper therefore deserves publication in a high standard journal such as Nature communication but answering the following questions could improve the quality of the manuscript.
- The scope of substrates is limited to cyclobutanols with aryl substituents and a few thiophene derivatives. Only one non-aromatic cyclobutanol is included but still contain a phenyl substituents in its structure. Could the reaction be performed in a more general manner using cyclopentanols or cyclohexanols? Is the presence of a large substituents on the cyclobutanols necessary or a simple methyl or ethyl derivatives could be efficiently transformed?
- The role of the phosphine ligands in the tuning of the selectivity remains unclear. Could the authors explain or give their thoughts on how the properties of the ligands increase selectivity to one product or the other?

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The requested changes have been properly addressed and consequently the manuscript is, in my opinion, suitable for pubblication on Nature Communications.

Reviewer #2

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

Reviewer #4

(Remarks to the Author)
In view of the changes made by the authors and the justifications provided, I now think that the revised manuscript can be published in Nature Communications.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Recommendation: The proposed work could be considered for publication in Nature Communications after major revision.

General Comment: In this manuscript, X.-F. Wu and co-workers report a novel divergent palladium-catalyzed carbonylation strategy for the synthesis of less common bicyclic nitrogen-containing heterocycles, enabled by the judicious choice of phosphorus ligands. The methodology exhibits a broad substrate scope and good tolerance toward a wide range of functional groups. Additional value is provided by the successful functionalization and derivatization of pharmaceutically relevant and naturally occurring compounds. Mechanistic insight is supported by well-designed control experiments, which suggest the involvement of a common key intermediate that can be selectively converted into the desired products under standard reaction conditions. Moreover, deuterium-labeling experiments further corroborate the proposed reaction mechanism. Overall, the manuscript is clearly written, and in most cases the experimental data are reported in an appropriate and rigorous manner. Taken together, this study represents a valuable contribution to the field of palladium-catalyzed carbonylation chemistry and will be of broad interest to the scientific community. For these reasons, I recommend publication in Nature Communications after major revision. Detailed comments are provided below.

Thanks for your kind and valuable comments! Thank you!

Additional Comments:

• To provide a more comprehensive overview of the state of the art, the authors are encouraged to cite relevant literature in the main text, including: Schiroli et al. (doi: 10.1002/adsc.202401183), describing a palladium-catalyzed carbonylative approach to nitrogen heterocycles with further derivatization toward peptide synthesis. Pancrazzi et al.(Org. Lett. 2020, 10.1021/acs.orglett.0c00171), reporting a double cyclization strategy in carbonylation reactions to enhance molecular complexity.

Sorry for the missed achievements. They have been cited as Ref 76 and 77.

• In the Supporting Information, the resolution of several molecular structure figures is poor and should be improved.

Thanks! They have been checked and corrected.

• The 1H and 13C-NMR spectra of compound 3c appear to be inverted.

Thanks! They have been checked and corrected.

• The purity of compounds 3f, 3u (notably in the 1.5–1.0 ppm region), 3ab, and 3ak could be improved.

Thanks! We do need your understanding in this case. That was due to the trace amount of polymer in eluent we used which is not possible to remove. The polymer was added by our supplier to quench radical generated during storage. They could be detected in ^{1}H NMR, but not in ^{13}C NMR. In order to avoid any misleading, a statement of purity has been added in ESI.

• In several NMR spectra, proton integrations are reported twice in the spectra, and integrations are also included in the 13C-NMR spectra. Please clarify whether there is a specific reason for this representation.

Thanks! The duplicated ^{13}C resonances and minor duplication of certain ^{1}H signals are attributed to slowly interconverting amide rotamers; no diastereomeric mixture was detected by ^{1}H NMR. An explication has been added in ESI.

Reviewer #2 (Remarks to the Author):
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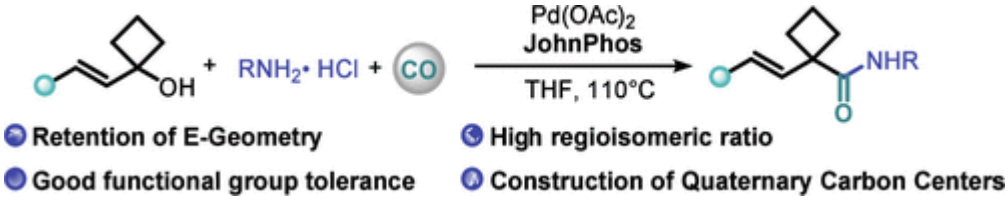
Thanks for your kind and valuable comments! Thank you!

Reviewer #3 (Remarks to the Author):
The manuscript describes a palladium-catalyzed, ligand-directed dicarbonylation of cyclobutenols, CO, and amines to afford 3-azabicyclo[3.2.0]heptane and 3-azabicyclo[3.1.1]heptane scaffolds in low to moderate yields. This reaction was similar to the authors' previous work on palladium-catalyzed aminocarbonylation of vinylcyclobutanols for the synthesis of α-substituted β,γ-unsaturated cyclobutanecarboxamides (Org. Lett. 2025, 27, 11644). The current study only extends their previous work by replacing vinylcyclobutanol with cyclobutanol to produce β,γ-unsaturated cyclobutanecarboxamide, which further undergoes intramolecular palladium-catalyzed hydroamidocarbonylation. In fact, the similar intramolecular palladium-catalyzed hydroamidocarbonylation procedure has also been reported by Dong and coworkers (Angew. Chem. Int. Ed. 2024, 63, e202410967; J. Org. Chem. 2023, 88, 5036), although the authors did not cite these two references. The proposed catalytic cycle is not substantiated by experimental or computational evidence that distinguishes it from the mechanism already outlined in their earlier cyclobutanol work. The key question such as how the ligand structure controls the regioselectivity is not addressed beyond empirical observation. This manuscript just applies an analogous mechanism (Pd-hydride formation, alkene insertion, CO migration, and nucleophilic attack by an amine) to a similar substrate class, without introducing a new activation mode, a novel ligand design, or a stereocontrol strategy. Therefore, this manuscript lacks novelty and does not provide the depth of mechanistic insights required for a high-level journal. It does not belong in the Nature Communications.

Thanks for your time and comments in any case!
The three mentioned literatures have been shown behind, we can find out the significant difference easily.
Org. Lett. 2025, 27, 11644



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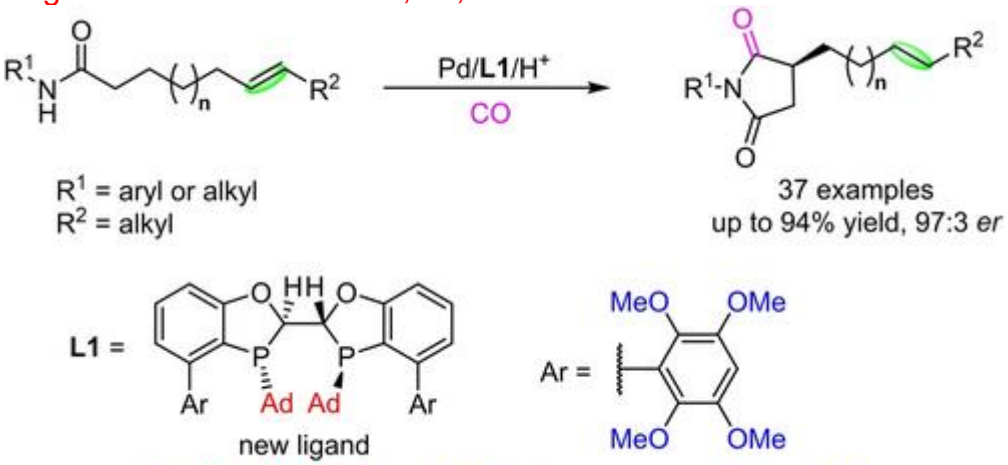

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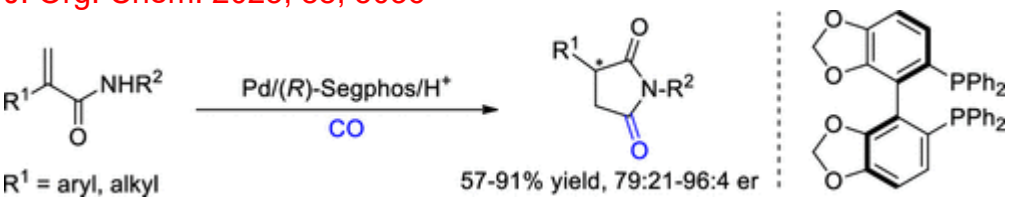

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Wu and co-workers report on the synthesis of distinct N-bridged heterobicycles via Pd-catalysed dicarbonylation processes from a strained four membered ring substrate. The manuscript is very interesting, and the study is well performed and includes a mechanistic investigation explaining the formation of both types of products. The scope of substrate used in large and moderate to high yields were obtained in most cases. The authors also demonstrate the potential of these systems to access biomolecule scaffolds of interest and using a model substrate, they show the derivatives that can be obtained from the dicarbonyl products formed during catalysis. The paper therefore deserves publication in a high standard journal such as Nature communication but answering the following questions could improve the quality of the manuscript.

Thanks for your kind and valuable comments! Thank you!

- The scope of substrates is limited to cyclobutanols with aryl substituents and a few thiophene derivatives. Only one non-aromatic cyclobutanol is included but still contain a phenyl substituents in its structure. Could the reaction be performed in a more general manner using cyclopentanols or cyclohexanols? Is the presence of a large substituents on the cyclobutanols necessary or a simple methyl or ethyl derivatives could be efficiently transformed?

Thanks for your professional comment! Other size of rings, such as cyclopentanol and cyclohexanol were tested, but the substrates stay as it was and lead to no desired product detectable. A statement has been added in the main text.

- The role of the phosphine ligands in the tuning of the selectivity remains unclear. Could the authors explain or give their thoughts on how the properties of the ligands increase selectivity to one product or the other?

Thanks for your professional comment! As shown in Scheme 7, our control experiments, for the formation of intermediate 14, both ligands can lead to the same product. In this step, we believe the double bond of cyclobutene also coordinate to Pd and diminished the tuning effect of ligands. For the second CO insertion, the effect of ligand become obvious: bidentate ligand react at less steric position and lead to product 3a; while monophosphine ligand reacted at benzylic position and lead to product 4a. A statement has also been added in the main text.