

Ligand-Controlled Regiodivergent Aminocarbonylation of Cyclobutanols toward 1,1- and 1,2- Substituted Cyclobutanecarboxamides



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REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Four-membered carbocycles are important skeletons widely found in bioactive molecules. Although several methods have been developed for the synthesis of this structural motifs, there are still several limitations remained, including limited substrate scope, cumbersome synthesis of starting materials and moderate selectivities. In this manuscript, Wu and coworkers have presented a palladium-catalyzed aminocarbonylation of cyclobutanols with anilines. By precise choice of the ligand, both 1,1 and 1,2-substituted cyclobutanecarboxamides could be constructed with excellent regioselectivities and outstanding diastereoselectivities. Moreover, this reaction could further be applied to the late-stage modification of the bioactive molecules and drugs. Mechanistic investigations revealed that substituted cyclobutene should be the intermediate for these transformations, and the ammonolysis is probably the rate-determining step of route A. Overall, the authors have done an excellent job in presenting their manuscript, and adequately discussing their findings. In addition, the supporting information is also well-prepared. Since regiodivergent synthesis is attractive for diversity-oriented synthesis in pharmaceutical applications, I believe this work would have significant implications for both the catalytic synthesis and medicinal chemistry. Therefore, I would like to recommend publication of the manuscript in Nature Communications after addressing following issues.

1. There are some typos in the Figure 1. For example, fig. 1a, “inhibitors” should be “inhibitor”; fig. 1e, “funcational” should be “functional”.
2. What about the results if cyclobutanols containing an alkyl group at the C1-positions?
3. It's not suitable to label the products shown in Figure 6b with dr values since this method could only construct the racemic products and enantiopure starting materials were used. Maybe trans/cis ratio is a better way to describe the diastereoselectivity.
4. It's quite interesting that 3ax could also be obtained in good yield although with 2.8:1 dr. For this case, a tri- or tetra-substituted cyclobutene could be involved. Which one would be the major intermediate?
5. The authors are encouraged to adjust the chemical shift range of ^{13}C spectra (for example, -10-220 ppm) so that the peaks could be shown cleared.

6. The NMR spectra for products 3b, 3f and 3ap were not clean.

7. Please provide the full carbon spectrum of product 3z.

Reviewer #2 (Remarks to the Author):

Wu and colleagues have reported a novel ligand-controlled regiodivergent aminocarbonylation of cyclobutanols with anilines and CO gas. This reaction exhibits high efficiency and regioselectivity, enabling the incorporation of a broad range of substrates and displaying excellent tolerance toward diverse functional groups. The choice of Nixantphos promotes to offer 1,2-substituted cyclobutanecarboxamides with trans-dia stereoselectivity, while (4-CF₃C₆H₄)₃P favors to afford 1,1-substituted cyclobutanecarboxamides. Furthermore, various valuable pharmaceutical molecules accessed by this protocol enhances the synthetic value of this methodology. Experimental mechanistic studies have shed light on the potential intermediates involved in the carbonylation process. This thorough investigation provides valuable insights into the reaction mechanism. It is undoubted that this work should provide an available strategy for the synthesis of these valuable compounds, and is quite interesting to the synthetic chemists to some extent. Therefore, the manuscript is suitable for publication in Nature Communication, provided the authors can address specific questions listed below:

1. The research as such has been competently carried out although I have to say that I missed the details on the pressure of CO gas (it is different in two process) and other optimization in the manuscript (as well as in the SI).
2. I am wondering that if this protocol is suitable for alkyl-substituted cyclobutanol or heterocyclobutanol. Even though it doesn't work, this information would extremely important, please include it.
3. Have any other byproducts during condition optimization, such as cyclobutene 26 been observed?
4. I am curious about if this protocol is suitable for cyclopropanol or cyclopentanol?

5. The SI is of high-quality. But there is a small error that I hope the author can verify, which is the polarity of the column chromatography of compound 22 (It is different on S39 and S42).

Reviewer #3 (Remarks to the Author):

The authors described the ligand-controlled regiodivergent aminocarbonylation of cyclobutanols toward 1,1- and 1,2-substituted cyclobutanecarboxamides, in which cyclobutanols was used as cyclobutene surrogate. The method exhibits good functional group compatibility, as well as high regio- and stereoselectivity, offering new pathways for synthesizing cyclobutanecarboxamides. However, the use of substituted alcohol as the olefins surrogate for carbonylation is a known protocol (Angew. Chem. Int. Ed. 2017, 56, 6203-6207). In addition, the relationship between ligand's structure and catalytic performance is not well investigated. Therefore, this reviewer would not recommend this work for publication in Nature Communications.

1. The authors proposed that bite angle of the bisphosphine ligand had an effect on the aminocarbonylation of cyclobutanols. The 1,2-substituted cyclobutanecarboxamides (3a) was obtained in 77% yield with 8:1 rr with Nixantphos and the bite angle of the Nixantphos ligand is 120 o. When the bite angle of the bisphosphine ligand reached 138 o, a large amount of 1,1- substituted cyclobutanecarboxamides (4a) was obtained. What is the result about bisphosphine ligand' bite angle between 120 o to 138 o. Furthermore, how the bite angle of the bisphosphine ligand affected the activity and selectivity of the Pd catalyst?
2. The authors said that “larger bite angle of DBFphos and the ligand's tendency to lean toward monophosphine ligands”. It is not convincing.
3. The investigation of substrate scope showed that aromatic ring in the cyclobutanols is necessary. What is the role the aromatic ring in aminocarbonylation of cyclobutanols?
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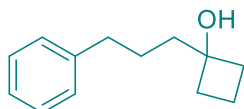
Thanks for your kind and valuable comments!

1. There are some typos in the Figure 1. For example, fig. 1a, “inhibitors” should be “inhibitor”; fig. 1e, “funcational” should be “functional”.

Thanks! They have been checked and corrected.

2. What about the results if cyclobutanols containing an alkyl group at the C1-positions?

Thanks! As suggested, an example of such cyclobutanol was prepared and tested, but no desired product was detected. A statement has been added in the main text.



3. It's not suitable to label the products shown in Figure 6b with dr values since this method could only construct the racemic products and enantiopure starting materials were used. Maybe trans/cis ratio is a better way to descript the diastereoselectivity.

Thanks! It's been corrected as suggested.

4. It's quite interesting that 3ax could also be obtained in good yield although with 2.8:1 dr. For this case, a tri- or tetra-substituted cyclobutene could be involved. Which one would be the major intermediate?

Thanks! We think tri-substituted cyclobutene could be involved as the major intermediate, but we got no direct prove in this case.

5. The authors are encouraged to adjust the chemical shift range of ^{13}C spectra (for example, -10-220 ppm) so that the peaks could be shown cleared.

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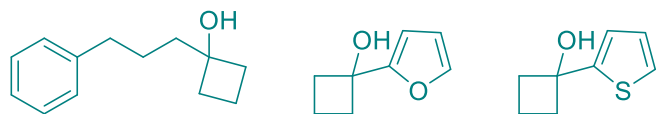
1. The research as such has been competently carried out although I have to say that I missed the details on the pressure of CO gas (it is different in two process) and other optimization in the manuscript (as well as in the SI).

Thanks! As shown in Figure 2, the pressure of CO can be decreased to 6 bar with similar results.

2. I am wondering that if this protocol is suitable for alkyl-substituted cyclobutanol or heterocyclobutanol. Even though it doesn't work, this information would extremely

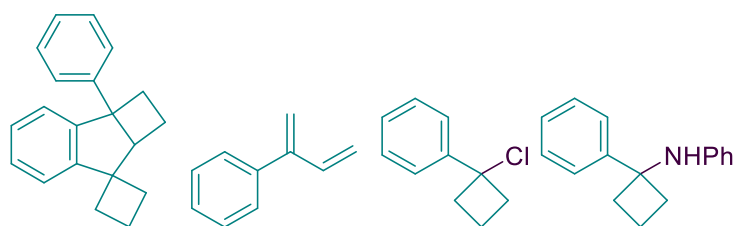
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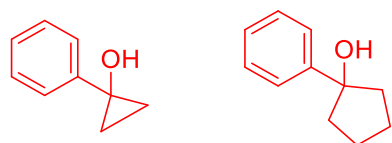
3. Have any other byproducts during condition optimization, such as cyclobutene 26 been observed?

Thanks! Several byproducts were detected during the optimization process. A statement has been added in the main text.



4. I am curious about if this protocol is suitable for cyclopropanol or cyclopentanol?

Thanks! We tested cyclopropanol and cyclopentanol analogues, but without desired amide detectable. A statement has been added in the main text.



5. The SI is of high-quality. But there is a small error that I hope the author can verify, which is the polarity of the column chromatography of compound 22 (It is different on S39 and S42).

Thanks! It's been corrected as suggested.

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performance is not well investigated. Therefore, this reviewer would not recommend this work for publication in Nature Communications.

Thanks for your comments! The mentioned work (Angew. Chem. Int. Ed. 2017, 56, 6203-6207) from Beller's group is on linear esters synthesis which cannot control the selectivity either. We are producing amides here with linear and branch control. The using of amine as the nucleophile is significantly more challenge.

1. The authors proposed that bite angle of the bisphosphine ligand had an effect on the aminocarbonylation of cyclobutanols. The 1,2-substituted cyclobutanecarboxamides (3a) was obtained in 77% yield with 8:1 rr with Nixantphos and the bite angle of the Nixantphos ligand is 120 o. When the bite angle of the bisphosphine ligand reached 138 o, a large amount of 1,1- substituted cyclobutanecarboxamides (4a) was obtained. What is the result about bisphosphine ligand' bite angle between 120 o to 138 o. Furthermore, how the bite angle of the bisphosphine ligand affected the activity and selectivity of the Pd catalyst?

Thanks! This is related with the stability of the intermediate and at which side of the alkene should insert. The bisphosphine ligand with 138 o bite angle is more like a monophosphine ligand and lead 4a as the main product. Bisphosphine ligand with proper bite angle produce stable palladium intermediate which is steric and lead the less-bulky position of alkene with 3a as the main product.

2. The authors said that "larger bite angle of DBFphos and the ligand's tendency to lean toward monophosphine ligands". It is not convincing.

Thanks! It's like DPPPe, more like monophosphine ligand. When the bite angel too large, the mental center become not steric or even mono-coordinated which behavior more like monophosphine ligand. For example: <https://pubs.rsc.org/en/content/articlelanding/1983/c3/c39830001308#!divCitation>.

3. The investigation of substrate scope showed that aromatic ring in the cyclobutanols is necessary. What is the role the aromatic ring in aminocarbonylation of cyclobutanols?

Thanks! Here the aromatic ring makes the dehydration step easier and to facile alkene formation and palladium hydride insertion.

4. How about the reaction with other acyclic alcohol?

Thanks! This work is focused on the preparation of cyclobutene based amides. For acyclic alcohol, both reaction efficiency and selectivity decreased under these conditions. A statement has been added in the main text.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors have addressed the concerns raised in the revisions. Therefore, I would like to support its publication as it is.

Reviewer #2 (Remarks to the Author):

The revised manuscript has addressed all my previous concerns, please publish it.

Reviewer #3 (Remarks to the Author):

The manuscript has been improved, and I support its publication in the current form.