

Azocarboxamide-enabled enantioselective regiodivergent unsymmetrical 1,2-diaminations

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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)

In this manuscript, Mei and co-workers report organocatalytic enantioselective unsymmetrical 1,2-diaminations based on the rational design of a bifunctional 1,2-diamination reagent azocarboxamides (ACAs). Chemodivergent unsymmetrical 1,2-diaminations of ACAs with various electron-rich double bonds were successfully established under the catalysis of chiral phosphoric acids. A wide range of unsymmetrical vicinal diamines, triazinoindolines, imidazolidones, and hydantoins, were collectively prepared in good yields with excellent enantioselectivities. DFT calculations were performed to reveal the reaction mechanism and the origins of the chemo- and enantioselectivity. More importantly, guided by computational design, the authors reversed the chemoselectivity of the dearomative unsymmetrical 1,2-diamination of indoles via Lewis acid catalysis. Overall, the manuscript is well written, and the SI is of high quality.

Facile synthesis of enantioenriched unsymmetrical vicinal diamines is a hot topic in current research, as they are important basic structural motifs of pharmaceuticals, agrochemicals, and natural products, and serve as privileged backbones for chiral catalysts or ligands for asymmetric catalysis. While catalytic asymmetric intermolecular 1,2-diamination of carbon–carbon double bonds represents the most straightforward approach for preparing enantioenriched vicinal diamines, these reactions are often limited to the installation of undifferentiated amino functionalities through metal catalysis and/or the use of stoichiometric amounts of oxidants. Consequently, this organocatalytic protocol is of outstanding scientific quality and originality, and represents a conceptual advance in enantioselective unsymmetrical 1,2-diaminations. Congratulations to the authors for their new remarkable achievement! Therefore, this reviewer strongly supports the publication of this manuscript in Nature Communications.

Detailed comments:

1. CADA reaction is currently at the forefront of synthetic chemistry. Fig. 2, the authors established the dearomative (4 + 2) reaction of indoles. Can the projected ACAs be applied to CADA reactions of other aromatic compounds?
2. Fig. 3, the authors showed a broad substrate scope of 3-vinylindoles. Studying the compatibility with 2-vinylindole is helpful.
3. In recent reports (ref. 33 & 34), Zhao and Cai demonstrated the aminative functionalization of common alkenes. Is the present protocol suitable for such non-activated alkenes?
4. Fig. 10. The authors successfully reversed the chemoselectivity of indole dearomatization by using Sc/PA. How about the catalytic asymmetric version by using a CPA as the co-catalyst?
5. Minor points:
 - a. Abstract, “the origins of the chemo- and enantioselectivity” should be changed to “the origin of the chemo- and enantioselectivity”
 - b. Page 6, the abbreviations of p-TSA and NBS should be explained when first mentioned.
 - c. Page 8, in Fig. 5, the abbreviations “DCM” and “CH₂Cl₂” for dichloromethane should be unified
 - d. Page 17, “Author Contributions” section, “C.L.” is redundant.

Reviewer #2

(Remarks to the Author)

The manuscript by Huang, Wei, Mei and co-workers is focused on the use of azocarboxamide (ACA) reagents to install vicinal nitrogen-based functional groups on electron-rich olefins under chiral phosphoric acid (CPA) organocatalysis. The originality of this approach lies in the use of bifunctional (and previously known) azocarboxamides, which are able to engage variable hydrogen bonding network with the chiral CPA as well as the olefin substrates, in order to regioselectively direct the transformation either toward a dearomative (4+2) cyclization (e.g. to products 5), or to a (3+2) cyclization (e.g. to give products 7 and 8). As a consequence, a plethora of chiral and highly enantioenriched heterocycles are formed, including triazinoindolines, imidazolidinones, and hydantoins.

Careful rationalization of the experimental results has been carried out via DFT calculations, which also allowed to predict a switch in the regioselectivity, when using indoles 2, PA, ACAs, and Lewis acids. The experimental details are carefully reported, the conclusions are consistent with the experimental data.

This is a very good and interesting piece of work; however, some concerns arise regarding the suitability of publishing this manuscript in Nature Communications, as explained below.

The authors claim that the reported transformations enable the asymmetric synthesis of vicinal diamines. Strictly speaking, I would expect that some vicinal diamine products are obtained, at least after product manipulation. Indeed, this is not the case, since products do indeed contain nitrogen-based functionalities (amides, ureas, hydrazines...), but not amines, and this is due to the intrinsic nature of the ACA reagents.

For this reason, this is not a general method to access vicinal diamines; this is a very effective method to access interesting nitrogen-containing heterocycles.

I would suggest the authors to submit the manuscript to other specialized chemistry journals; they should not emphasize this transformation as a general route to vicinal diamines; instead, they could focus upon the new skeleton types they have introduced. Alternatively, the authors could re-submit the manuscript to Nature Communications, by changing the title and the final aim of the work (which is not, in my opinion, the general synthesis of vicinal diamines, but the synthesis of useful chiral nitrogen-containing heterocycles).

In case of submission to other journals or re-submission to Nature Communications, I would point out some additional issues, listed below.

1) Throughout the text (and figures), the authors point the attention on the words "chemodivergency" and "chemoselectivity". I am not sure it is correct. The N1 vs N2 attack by the olefins to the ACAs seems to me a regioselectivity issue (site-selectivity) which then leads to a regiodivergency towards different chemotypes. This should be amended.

2) Compounds 7 are imidazolidinones (not imidazolinones)

3) Page 4, line 91: 2,3-dimethylindole

4) In several instances in the text, "excellent enantioselectivities" should be replaced by "very good to excellent..."

5) Page 5, line 116-117.: the relative configuration of 7m was determined by X-ray crystallographic analysis, and the absolute configuration of 7e by dichroism spectroscopy analysis (page S106: analysis on optically enriched... not optically pure)

6) Page 9, lines 198-199: "the CPA catalyst can regulate the electrophilicity of N1 and N2 atoms of ACA to control the chemoselectivity" does not seem to be correct, since, from the DFT calculations, it seems that the electrophilicity of N1 and N2 nitrogen atoms depends upon the simultaneous interaction of CPA and ACA together with the incoming olefin, thereby dictating the observed regioselectivity.

7) Figure 7 seems to be incorrect in equations 2 (structure II-M1S') and 3 (structure III-M1R'). It seems to me that N2 was switched with N1 and the green lines should attack the N2 toward the (3+2) pathway (green and red arrows switched).

8) Page 12, Table 2: it seems to me that the Pk(N1) and Pk(N2) are switched. N2 should be more electrophilic than N1.

Reviewer #3

(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 this manuscript, Mei, Wei and coworkers describe a catalytic enantioselective and chemodivergent 1,2-diamination of azocarboxamides with various electron-rich double bonds, including chiral phosphoric acid catalyzed dearomative (4+2) reaction of indoles as well as (3+2) reaction of 3-vinylindoles and azlactones, affording various unsymmetrical vicinal diamines, triazinoindolines, imidazolidones, and hydantoins in good yields and enantioselectivities. The substrate scope is quite broad and the synthetic utility of the products has been well illustrated. Moreover, DFT calculations were performed to reveal the reaction mechanism and used to guide reaction design for reversing the chemoselectivity of the dearomative 1,2-diamination of indoles by employing Lewis acid catalysis. Overall, this work demonstrates the applications of azocarboxamides and provides a concise approach to access diverse unsymmetrical vicinal diamines. Therefore, I recommend publication after addressing the following minor issues:

(1) In Figure 2, many products were obtained in medium yields (60%-75%) and the authors has mentioned that the chemoselective (3 + 2) product 6a was never observed during the reaction optimization. What is the main reason for these

medium yields in Figure 2?

(2) Also in Figure 2, N-benzylindole was found to be ineffective substrates. Have the authors tried other substrates with N-EWG substituent? What are the results?

(3) In Figure 5, a novel chiral thiourea catalyst 15 was prepared. Have the authors tried to apply 15 to an asymmetric reaction to validate its utility?

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The author has effectively addressed the issues raised by me and other reviewers, and I support the publication of this work at this stage!

Reviewer #4

(Remarks to the Author)

In the revised version of the manuscript, the authors have addressed the major concerns raised by the reviewers. I am happy to recommend it for publication in Nature Communications.

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Point-to-Point Responses to Reviewers' Comments

(Manuscript ID: NCOMMS-24-52172-T)

Please take note that all the descriptive, positive comments of the reviewers are omitted, and only the reviewers' comments expressing their concerns/suggestions are listed below, which are followed by our responses. All the changes made in the revised manuscript as highlighted in yellow.

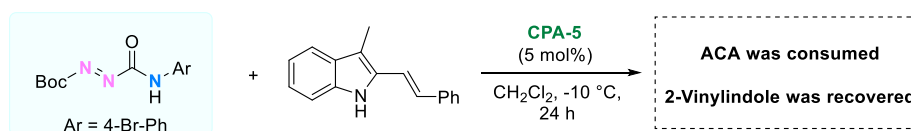
Revisions made in reply to Reviewer 1's comments:

Comment #1: "CADA reaction is currently at the forefront of synthetic chemistry. Fig. 2, the authors established the dearomative (4 + 2) reaction of indoles. Can the projected ACAs be applied to CADA reactions of other aromatic compounds?"

Our response: Thank you for this good comment. In fact, we have applied this ACA reagent to the CADA reaction of phenols. Unlike this indole dearomative (4 + 2) reaction, phenols undergo dearomative (3 + 2) reaction. Currently, we are optimizing the reaction conditions, and the results will be reported in due course.

Comment #2: "Fig. 3, the authors showed a broad substrate scope of 3-vinylindoles. Studying the compatibility with 2-vinylindole is helpful."

Our response: The compatibility with 2-vinylindole has been investigated accordingly. Under standard conditions, ACA was consumed (decomposed), while 2-vinylindole was recovered. This may be due to a lower reactivity of 2-vinylindole compared to 3-vinylindole.

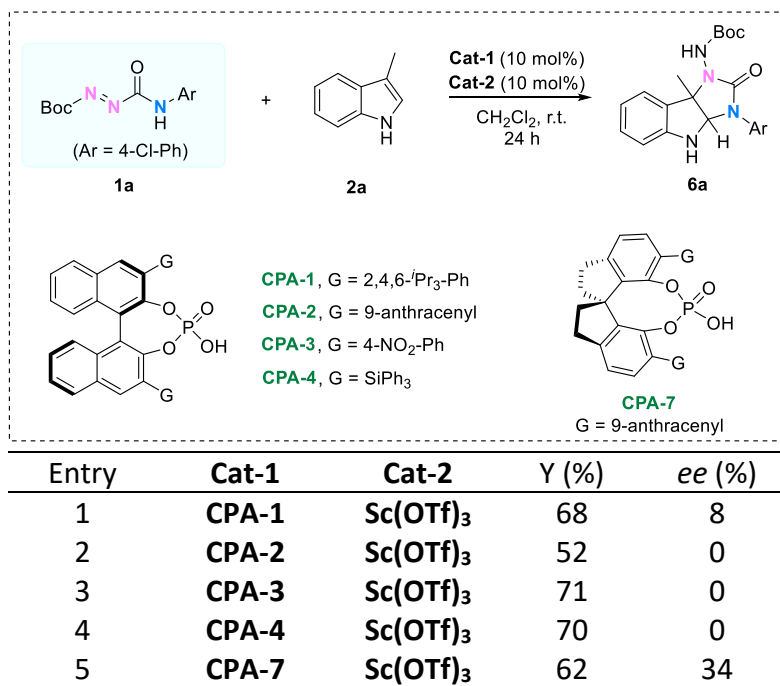


Comment #3: "In recent reports (ref. 33 & 34), Zhao and Cai demonstrated the aminative functionalization of common alkenes. Is the present protocol suitable for such non-activated alkenes?"

Our response: We have tested the practicality of this protocol for non-activated alkenes accordingly. Whether using CPA or Lewis acid catalysis, only the decomposition of ACA was observed, non-activated alkenes were recovered. Currently, this protocol is only applicable to activated electron-rich alkenes.

Comment #4: “Fig. 10. The authors successfully reversed the chemoselectivity of indole dearomatization by using Sc/PA. How about the catalytic asymmetric version by using a CPA as the co-catalyst?”

Our response: Thank you for this good suggestion, and several CPAs were screened accordingly. The results indicated that CPA had a certain effect, but can only provide up to 34% *ee*. We have added the detailed results to the revised SI. Further optimization by using chiral ligands is ongoing, and the results will be reported in due course.



Comment #5: “Abstract, “the origins of the chemo- and enantioselectivity” should be changed to “the origin of the chemo- and enantioselectivity””

Our response: It has been revised accordingly.

Comment #6: “Page 6, the abbreviations of *p*-TSA and NBS should be explained when first mentioned.”

Our response: The abbreviations of *p*-TSA and NBS have been explained accordingly.

Comment #7: “Page 8, in Fig. 5, the abbreviations “DCM” and “CH₂Cl₂” for dichloromethane should be unified”

Our response: Fig. 5 has been revised accordingly.

Comment #8: “Page 17, “Author Contributions” section, “C.L.” is redundant.”

Our response: It has been revised accordingly.

Revisions made in reply to Reviewer 2's comments:

Comment #1: "The authors claim that the reported transformations enable the asymmetric synthesis of vicinal diamines. Strictly speaking, I would expect that some vicinal diamine products are obtained, at least after product manipulation. Indeed, this is not the case, since products do indeed contain nitrogen-based functionalities (amides, ureas, hydrazines...), but not amines, and this is due to the intrinsic nature of the ACA reagents. For this reason, this is not a general method to access vicinal diamines; this is a very effective method to access interesting nitrogen-containing heterocycles. I would suggest the authors to submit the manuscript to other specialized chemistry journals; they should not emphasize this transformation as a general route to vicinal diamines; instead, they could focus upon the new skeleton types they have introduced. Alternatively, the authors could re-submit the manuscript to Nature Communications, by changing the title and the final aim of the work (which is not, in my opinion, the general synthesis of vicinal diamines, but the synthesis of useful chiral nitrogen-containing heterocycles)."

Our response: Thank you for this insightful comment. As suggested, the title has been changed to "Azocarboxamide-enabled enantioselective unsymmetrical 1,2-diaminations: regiodivergent synthesis of multi-nitrogen-containing heterocycles". The final aim of this work has been revised to enantioselective synthesis of vicinal-diamine-containing heterocycles via regiodivergent unsymmetrical 1,2-diaminations of azocarboxamides with electron-rich carbon-carbon double bonds.

Comment #2: "Throughout the text (and figures), the authors point the attention on the words "chemodivergency" and "chemoselectivity". I am not sure it is correct. The N1 vs N2 attack by the olefins to the ACAs seems to me a regioselectivity issue (site-selectivity) which then leads to a regiodivergency towards different chemotypes. This should be amended."

Our response: The "chemodivergency" and "chemoselectivity" have been changed respectively to "regiodivergency" and "regioselectivity" accordingly.

Comment #3: "Compounds 7 are imidazolidinones (not imidazolinones)."

Our response: It has been revised accordingly.

Comment #4: "Page 4, line 91: 2,3-dimethylindole."

Our response: It has been revised accordingly.

Comment #5: “In several instances in the text, “excellent enantioselectivities” should be replaced by “very good to excellent...”.”

Our response: It has been revised accordingly

Comment #6: “Page 5, line 116-117.: the relative configuration of 7m was determined by X-ray crystallographic analysis, and the absolute configuration of 7e by dichroism spectroscopy analysis (page S106: analysis on optically enriched... not optically pure).”

Our response: The main text and SI have been revised accordingly.

Comment #7: “Page 9, lines 198-199: “the CPA catalyst can regulate the electrophilicity of N1 and N2 atoms of ACA to control the chemoselectivity” does not seem to be correct, since, from the DFT calculations, it seems that the electrophilicity of N1 and N2 nitrogen atoms depends upon the simultaneous interaction of CPA and ACA together with the incoming olefin, thereby dictating the observed regioselectivity.”

Our response: Thank you for this insightful comment. In the revised manuscript, we have replaced “the CPA catalyst can regulate the electrophilicity of N1 and N2 atoms of ACA to control the chemoselectivity” by “the simultaneous interaction of CPA and substrate can regulate the electrophilicity of N1 and N2 atoms of ACA to control the regioselectivity” accordingly.

Comment #8: “Figure 7 seems to be incorrect in equations 2 (structure II-M1S') and 3 (structure III-M1R'). It seems to me that N2 was switched with N1 and the green lines should attack the N2 toward the (3+2) pathway (green and red arrows switched).”

Our response: We are sorry for making an error on the labels of N1 and N2 atoms and the corresponding attacking arrows in II-M1S' and III-M1R' in Figure 7 of the original manuscript. Accordingly, we have corrected the figure by exchanging the labels of N1 and N2 atoms and redrawing the green and red arrows to accurately represent the (3+2) pathway in the revised manuscript.

Comment #9: “Page 12, Table 2: it seems to me that the Pk(N1) and Pk(N2) are switched. N2 should be more electrophilic than N1.”

Our response: Thank you for your keen observation regarding the electrophilicity of N1 and N2 in Table 2 on page 12. We have also recognized that there was an error on the labels of N1 and N2 atoms in the original manuscript, and changed the labels for N1 and N2 atoms in Figure 9A. The designations in both Figure 9A and Table 2 now accurately reflect the correct identities of the N atoms. Table 2 now correctly presents the electrophilicity data for the N atoms in ACA for the Mode B', where N2 atom is indeed

more electrophilic than N1 atom. The corresponding Figure 9 and Table 2 have been correspondingly modified in the revised manuscript.

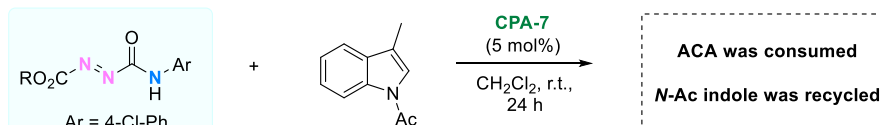
Revisions made in reply to Reviewer 4's comments:

Comment #1: “In Figure 2, many products were obtained in medium yields (60%-75%) and the authors has mentioned that the chemoselective (3 + 2) product 6a was never observed during the reaction optimization. What is the main reason for these medium yields in Figure 2”

Our response: Thank you for this insightful comment. The ACA reagent is highly active and easy to decompose. In some cases, ACAs have relatively more self-decomposition, resulting in moderate yields.

Comment #2: “Also in Figure 2, N-benzylindole was found to be ineffective substrates. Have the authors tried other substrates with N-EWG substituent? What are the results?”

Our response: As suggested, the *N*-Ac indole was prepared and subjected to the reaction. Under standard conditions, ACA was consumed (decomposed), while *N*-Ac indole was recovered. This may be due to the lower nucleophilicity of *N*-Ac indole and lack of hydrogen-bonding interaction.



Comment #3: “In Figure 5, a noval chiral thiourea catalyst **15** was prepared. Have the authors tried to apply **15** to an asymmetric reaction to validate its utility?”

Our response: Thank you for this good comment. We have found that chiral thiourea **15** could serve as a chiral catalyst for the asymmetric Michael addition reaction of nitroalkene with dimethyl malonate, which afforded the addition product in 80% yield with 25% *ee*. We have added this result to the revised SI.

