

March 7, 2019

Dear Editor,

Please find enclosed our revised manuscript entitled "Efficient Synthesis of All-Carbon Quaternary Centers via the Conjugate Addition of Functionalized Monoorganozinc Bromides" that we wish to submit for further review. We have analyzed the thoughtful suggestions from the reviewers and editorial staff at the *Journal of Visualized Experiments*, and have accordingly revised the manuscript to address those specific questions and comments. A point-by-point breakdown of all changes in the manuscript is detailed in the following points.

Editorial Comments:

- We have again proof-read the document and made minor changes to wording and/or spacing (see track changes).
- All images for this manuscript are original and have not been published before (specifically, reference 14).
- We have added four key words to total seven.
- Figure and Table titles have been expanded and properly formatted.
- The Table has been uploaded as a separate excel file. The scheme that appears as the table header has been uploaded as an individual .tiff image ("Table1 reaction").
- Several instances of the unit 'minutes' have been abbreviated to min.
- We have added the R_f values for the TLC analysis described in step 2.2, which originally appeared later in the document.

Reviewer's Comments:

- The column 2 header in Table 1 has been changed to the correct compound number.
- All references have been double-checked and name errors, pagination, and journal titles have been corrected.
- The reaction featured in this manuscript affords a racemic mixture of enantiomeric products because the enone is achiral (but prochiral), and the catalyst and organozinc reagent are also achiral. This includes all examples in Figure 4 *except 32–35*. Therefore, this is the only possible outcome and would not be classified as a stereoselective process. However, this reaction *is* stereoselective (and stereospecific) only when a chiral unsaturated ketone is employed such as **17–20** in Figure 1. These specific substrates are chiral and racemic, and the reaction products **32–35** afford a racemic mixture of diastereomers.

We note Reviewer #2's comments about the reaction stereoselectivity. As was implied in

our presentation of the reaction, since the substrates are themselves racemic as evident in Figure 1, and no other source of chirality exists in the reaction (organozinc or catalyst), a racemic mixture of products is implied. This is what we have done in Reference 14. To make the issue unambiguous, we have added (\pm) to the appropriate substrates and products in Figures 1 and 4. We have also modified the text at the end of page 4 to include a brief discussion of the racemic materials, as well as how the diastereomer ratios were generally measured. We are choosing to omit the specifics of each diastereomeric product (**32–35**) because those details have been published in Reference 14, and we feel that the representative product **21** is sufficient for characterization in the manuscript. If we would include any additional data for **32–35**, then the argument could be made to include all of the data for compounds in Figure 4. This data has been fully tabulate, along with images of spectra, in Reference 14.

Finally, we have also addressed the net result from the stereoselective additions at the end of the paragraph on page 4. We were not able to find a specific reference that discusses the model used to *explain* the stereochemical outcome, however, this type of addition is exceedingly common in copper-catalyzed conjugate addition reactions with organometallic reagents. We believe a statement of the outcome trend is more relevant to this manuscript, rather than a more in-depth analysis of why.

- We have included two recent references in the introductory paragraph related to conjugate additions that form quaternary stereocenters.
- Reviewer #2 asks about organozinc stability beyond 18 h, however, we are not able to comment on this because we have not performed this type of study. The time limit suggested was based on a brief observation. As we note near the end of the discussion section, this reaction is more efficient with *filtered organozinc* reagents, as detailed in Reference 14. This is the best option for long-term storage of an organozinc reagent. We have not added additional text to this manuscript to address the comment, but note the relevance of the question.
- We have performed a detailed time-course of GC traces that map the organozinc formation. While this would clearly demonstrate the formation of organozinc reagent, we are confident that the description in 1.2.1 is sufficient. We also have not performed an array of 2D NMR experiments to fully map out each proton and carbon in the structure, and therefore cannot label them in the structure beyond obvious differences in chemical shift.

Thank you in advance for your consideration of our revised manuscript.

Sincerely,



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