nature portfolio

Peer Review File

Deoxytrifluoromethylation/Aromatization of Cyclohexan(en) ones to Access Highly Substituted Trifluoromethyl Arenes

Editorial Note: this manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments and rebuttal letters for versions considered at *Nature Communications*.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

In this revised manuscript by Altman and coworkers, the authors have reported the conversion of cyclohexanones to their trifluoromethylarene counterparts. The authors have addressed many concerns raised by other reviewers and me. Specifically, they have shown that different heterocycles and some sensitive functional groups could be compatible with this protocol. In addition, they have highlighted the application of this strategy in the synthesis of pharmaceutically relevant molecules and convinced me that this protocol could complement existing trifluoromethylation reactions that mainly relied on cross-couplings. Therefore, this work is now suitable for publication at Nat Commun. A few minor suggestions:

1. The authors have done a great job demonstrating the synthetic utility of this deoxytrifluoromethylation method by showing the synthesis of potentially bioactive molecules. One example does not make too much sense to me is the modification of estradiol. I thought one could just easily convert the phenol group of estradiol to form the same product. Some discussion should be included.

2. The cif file and the Checkcif file should be uploaded for Nat Comm submission.

Reviewer #2 (Remarks to the Author):

Trifluoromethylarenes are an important class of fluorine-containing structures, so it is very important to develop efficient and convenient methods for synthesizing these compounds. Here, Altman and colleagues reported deoxytrifluoromethylation/aromatization of cyclohexan(en)ones to access highly substituted trifluoromethyl arenes. The cyclohexan(en)one substrates undergo a 1,2-addition reaction with the Ruppert-Prakash reagent (CF3TMS) followed by aromatization to deliver highly functionalized Ar–CF3 compounds in a one/two-pot sequence. The author addressed most of my concerns and suggestions. This reviewer acknowledges that the authors have provided a previously unreported pathway. Overall this work represents a complementarity of the reactions in the field and I therefore recommend this manuscript to be accepted in Nat.Com.

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Dear Reviewers,

We appreciate the thoughtful comments. Specifically, we appreciate the scientific discourse and willingness of the reviewers to acknowledge the innovation in the pathway (R2), the improvements in scope (R1), the ability of the strategy to access pharmaceutically relevant substructures (R1), and the complementarity of this work relative to currently available strategies including cross-coupling technologies (R1+R2).

In response to further comments from Reviewer 1:

Modification of Estradiol: We agree that the same Ar–CF_3 compound can be accessed from phenols or Ar–OX via cross coupling chemistry. The goal of this substrate (**28S**) is to demonstrate two aspects: i) corresponding cyclohexenone could be accessed via Birch Reduction of complex natural products and ii) the method tolerates complex natural products. We were able to demonstrate that estradiol upon Birch reduction afforded corresponding cyclohexanone, which was subjected to the deoxyfluoroalkylation/ aromatization sequence to deliver the desired Ar–CF_3 product (**28P**). Also, this strategy complements the established cross-coupling trifluoromethylation strategy. A note has also been added on the main text discussion.

Cif File and Checkcif File: Both files have been uploaded to the submission portal along with Main Texts and Supplementary Information.

We hope that you find the revised manuscript suitable for publication in *Nature Communications*!

Respectfully,

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