nature portfolio

Peer Review File

Halogencarbene-Free Ciamician-Dennstedt Single-Atom Skeletal Editing

Corresponding Author: Professor Xihe Bi

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, Bi and co-workers describe a Ciamician-Dennstedt reaction using α-halogen-free carbenes as the carbon source, converting indoles/pyrroles into structurally diverse quinoline/pyridine scaffolds. This method allows the introduction of fluoroalkyl, aryl, heteroaryl, alkenyl, alkynyl, and alkyl groups. The synthesis of several medicinally bioactive quinolines demonstrates the utility of their protocol. Control experiments and DFT calculation results indicate that the crucial 1,4-dihydroquinoline intermediate can undergo different pathways to yield various insertion products, depending on the carbene precursor and reaction conditions.
The authors propose the use of α-halogen-free carbenes. A recent work by Glorius (Nat Catal, 2024, 7, 242–251) used α-iodonium diazo compounds with various functional groups as the carbon source for ring expansion. However, the carbene reagent in this study is simpler, and their previous work (Angew. Chem. Int. Ed, 2024, 63, e202313807) has enhanced the practicality of the agent. Compared to previous studies, although this work employs more complex and stringent reaction conditions, it enables the introduction of a broader range of functional groups.
In my opinion, the chemistry reported is interesting and suitable for publication in Nature Communications following minor revisions:
a) The manuscript employs N-TBS-protected indoles as substrates. How does the transformation perform with NH-indoles? Does it fail in these cases? b) The N-TBS-protected pyrroles do not yield the target products with copper(I) catalyst, yet the reaction of 1H-pyrrole works using Rh2(esp)2 as a catalyst. Please explain why. c) The manuscript does not report the reaction of N-triftosylhydrazones other than aryl N-triftosylhydrazones (e.g., trifluoroacetaldehyde N-triftosylhydrazone, pentafluoroethyl N-triftosylhydrazone, and alkyl, alkene, alkyne N-triftosylhydrazone) for 1H-pyrrole. How do these transformations perform? More clarity on these omissions and on reaction limitations, in general, would be appreciated. d) In Fig. 5a, the condition for step 2 is incorrect; it should be 25°C for 10 minutes. Corrections are also needed in the Supporting Information. In Fig. 2b, what does "Rf = F" mean? Is it CF3? This is not clear. Please verify this and ensure the manuscript is free from similar mistakes.

Reviewer #2

(Remarks to the Author)
Bi and co-workers report the ring expansion of N-silyl indoles to 3-functionalized quinolines. This is a very useful addition to the growing field of ‘molecular editing’ (Ciamician-Dennstedt) methods that have been reported recently, because it expands the scope of groups that be inserted from Ar (Bonge-Hansen, Levin, Ball) or halogen to include fluoroalkyl, vinyl, and formyl. The reaction also exhibits high FG compatibility, which for the arylative ring expansion surpasses the scope of the methods from Levin and Ball. The method is likely to be of broad interest to the synthetic community.

COMMENTS:

The introduction needs to be more balanced to avoid appearing misleading/disingenuous. For example, the use of metal carbenoids to effect ring expansion was reported by Bonge-Hansen, but this work is not discussed appropriately (instead it is thrown in to the general discussion of halocarbenes, which are not implicated in their work). Also, Bi et al have previously used the same strategy (and very similar reaction conditions) with ketone-derived Tfs hydrazones to effect ring expansion of indoles; the only difference in the present paper is that an aldehyde-derived hydrazone allows for oxidation of the ring

expansion product to a quinoline. Rather than trying to inflate the novelty of the present work (see also the comments on Fig 4), the authors should focus on fully explaining the practical benefits, which include the scope:
Throughout the scope (and especially in the discussion of the arylative expansion), the authors could really highlight the value of their work by discussing where it goes beyond the current state of the art defined by Levin and Ball. For example, Levin and Ball's chemistry isn't demonstrated for basic N (eg, azaindoles), aldehydes, acidic protons (eg, alcohols), alkenes, epoxides, vinylative expansions… This is a missed opportunity to really highlight the benefits of the present work that I encourage the authors to embrace.

Please discuss the thermal stability of the hydrazones in the manuscript, and re-state any issues in the SI.

Show the structure of the ligand at its first mention in the manuscript (eg, fig 1)

Show the structure of Tfs at its first mention in the manuscript

P5, L105: the claim that amine functional groups are tolerated is inaccurate; cpd 13 is a Boc-amine. The text should be changed to state "…protected amine (13)" or similar.

P5, L109: It is good that the limitations of the scope are noted ("3-methyl-TBS-indole produced ring expansion product 4 in ~20% yield."). However, it would be useful if the authors could comment on whether the failure of 3-substituted indoles in the fluoroalkylation is general (ie, are other 3-substituents tolerated under the conditions of Fig 2?). The authors should also state explicitly whether (a) 2-substituted indoles are tolerated in the fluoroalkylative ring expansion, and (b) whether pyrroles are compatible with the fluoroalkylative ring expansion (they are demonstrated only for the arylative expansion).

P7, L163: "…and pyridine substituents all successfully introduced in high yields". The pyridyl unit is inserted in 35%, which is not a high yield. Please adjust the text accordingly.

Fig 3: For cpd 106, please add a footnote to state that the SM was a doubly-TBS protected indol, and that the silyl ether is deprotected under the reaction conditions. Don't leave this detail only in the body text.

P7, L183: The authors could/should mention that tryptophol and melatonin are 3-substituted indoles, which is a motif not tolerated in the fluoroalkylative expansion.

P7, L197: "A brief survey of pyrrole scope revealed that 2-(trichloroacetyl)-1H-pyrrole provided the desired pyridine 126 in 59% yield, …" fig 3 shows cpd 126 as dichloroacetyl. Please check.

Fig 4: This figure is misleading. By drawing unfair comparisons between literature methods and the present method, it overexaggerates the relative benefit of the ring expansion (RE) chemistry. The literature methods are all shown going back to very simple commercial building blocks, resulting in high step counts and low yields. For example, for the first panel, the literature routes go through 3-bromoquinolin-7-ol, which is commercially available (but expensive). If you instead report the literature routes from this intermediate they are one step, and the yield of cpd 131 beats that of the ring expansion approach. Similarly, the ring expansion route does not account for preparation of the TBS-indoles (some are commercial/custom synthesis, but are very expensive), the hydrazone, the hydrazide, the ligand, or the catalyst.
This figure (and associated discussion/SI) must be amended to give a fairer comparison, based on starting materials of similar complexity and accounting for the synthesis of all necessary reagents or catalysts that are not commercial (and again, apply the same standards to what you consider 'commercial').

P9, L247: "indicating a kinetic isotope effect (kH/kD) of 3:1… and appear to suggest an internal 1,3-hydride shift, which may be the rate-determining step of the reaction." First, the observed KIE cannot be used to draw conclusions on the RDS of the reaction. The KIE has been measured from an intramolecular competition, so in isolation it can only be used to draw conclusions about a selectivity determining step. Please amend the discussion appropriately. Second, there is no strong evidence (from the experiments shown in Fig 5b) that the H transfer is "internal" (presumably 'intramolecular'?): the use of 1H NMR to measure distribution of D in cpd 56-d (reaction 2 in panel b) tells us the overall position of the D (ie, whether it is on the quinoline or in the formyl group), but not whether D has been transferred between molecules (ie, some molecules may have D at both positions, other molecules may have no D; the overall quinoline:formyl distribution is unchanged). This analysis can be done by looking at the isotope distribution in the the HRMS data (which is not presented in the SI) and correcting for 13C isotopomers. The outcome of this analysis should be presented in the manuscript to support either an inter- or an intramolecular H transfer.

P9, L248: "… an internal 1,3-hydride shift". 1,3-hydride shifts require an antarafacial topology, so do not occur. From the computational results it seems that the H transfer is mediated by CsF and DMSO, so this process presumably cannot be considered a 'pure' 1,3-H shift. Please adjust the terminology used (eg, to "a formal 1,3-hydride shift") to avoid confusion.

Fig 5b: kH/kD, not KH/KD.

P13, L353: "The methodology is general, straightforward, scalable…" This claim is questionable, and should be deleted: there are clear limitations to scope (eg, 2- or 3- substituted indoles in Fig 2) or FGs that are not tested (especially acidic/epimerizable groups), so it is not possible to claim generality. The 'straightforward' claim is not realistic because the reagents and catalysts have to be prepared. The 'scalable' claim is not realistic due to the use of NaH (gas evolution) and

fluorinated solvents (EU PFAS regulations).

Supp Info:
The authors should state how the following compounds were prepared (with characterization data & spectra), or where they were purchased from: silyl indoles / pyrroles, ligands, catalysts, Tfs hydrazide.

Reviewer #3

(Remarks to the Author)
In this manuscript, Bi, Anderson, Liu, and coworkers report a mechanistically distinct Ciamician-Dennsteadt (CD) reaction of indoles and pyrroles to access 3-functionalized quinolines and pyridines. Compared to reported approaches relying on halogenated carbenes, using functionalized N-triftosylhydrazones as carbene precursors enables a general platform for single-atom skeletal diversifications with numerous functionalities that were challenging to introduce with previous approaches. The reaction exhibits a broad substrate scope toward both components, with more than 130 3-functionalized quinolones synthesized. Moreover, access to 3-perfluoroalkylated quinolines as well as possible variations on carbene precursors make this method very general. The authors successfully applied this protocol for the total synthesis and late-stage skeletal modification of bioactive complex molecules, including drugs and natural products. It also provides experimental and theoretical evidence to support the proposed mechanism that proceeds via the formation of 1,4-dihydroquinoline intermediate and the origins of the chemoselectivity. Overall, the manuscript is well organized, the experiments conducted to a high standard, and the accompanying supporting information effectively supports the conclusion drawn in this study.
Since the single-atom skeletal editing of heteroarenes is a hot topic in current research, the findings reported here for the CD reaction of indoles and pyrroles using halogen-free carbene precursors deserve to be published in a high-ranking journal such as Nat. Commun. Hence, I strongly support its publication after addressing the following comments and suggestions. There are some issues that the authors should address before the publication of this work.
1. The late-stage single-atom skeletal editing of raputimonoindole B is quite interesting. Did the authors notice any competing cyclopropanation or ring expansion products of furan on the raputimonoindole B molecule?
2. Some alkene and alkyne functionalities were tolerated in the optimized protocol. Did the authors observe any [2+1] cycloaddition side reactivity? It might be interesting to comment on this.
3. In supplementary Fig. S18B, the authors explain the difference in Michael addition reaction outcomes of the CF3- and C2F5-substituted carbenes by comparing the electronegativity difference of O and C atoms in TS4 and TS4-1. However, I think it is more reasonable to make a comparison between the corresponding intermediates.
4. The authors need to check the structural formula of intermediate 148-d1 in Fig. 5b. It should be a H/D ligated to the N atom rather than a methyl group. In Figure 6a, the F atom is not shown in the structures of intermediate Int3 and transition state TS2. The authors should double-check the corresponding structure. Moreover, when DMSO was added to the free energy profile, the hydrogen bond between S and H was shown using dashed lines. However, I feel the O-H bond is more favored in this case. Have the authors considered the hydrogen bonding interaction between the O atom of DMSO and the H atom of the C-H bond?

Reviewer #4

(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.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
After thoroughly examining their responses to reviewer's comments and the changes made in the manuscript, I am pleased to see that they have addressed the feedback effectively to the paper. After careful consideration, I believe the manuscript is now suitable for publication.

Reviewer #2

(Remarks to the Author)
I am confident that the authors have addressed my comments - and those of the other reviewers - fully, and I am happy to recommend the article for publication in Nature Communications without further revision.

In particular, I am very grateful for the effort that the authors have put into expanding the scope of unsuccessful examples in their manuscript/SI: this diligence will be appreciated by the community.

Reviewer #3

(Remarks to the Author)
In this round of review, the authors conducted sound experimental studies and DFT calculations to address the reviewer's questions. Detailed explanations and responses are provided. I am glad to see the authors have adopted my suggestion and calculated the electronegativity between O and C atoms in Int9 and Int9-1. This data is more intuitive for understanding the origin of chemo-selectivity between CF3- and CF2CF3-substituted carbenes. Therefore, I suggest the authors move the data of electronegativity difference and stability comparison of allyl carbon anion intermediates (Supplementary Fig. 19) to the main text. These data can be used to replace Figure 6c as they are more interpretable. I would like to recommend the publication of this work in Nature Communications.

Reviewer #4

(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.

Point-by-point response to reviewer comments

Manuscript ID: NCOMMS-24-35130-T

Title: Halogencarbene-Free Ciamician-Dennstedt Single-Atom Skeletal Editing

Authors: Shaopeng Liu, Yong Yang, Qingmin Song, Zhaohong Liu,* Paramasivam Sivaguru, Yifan Zhang, Graham de Ruiter, Edward A. Anderson* and Xihe Bi*

Dear Reviewers,

Thank you very much for reviewing our manuscript and for kindly supporting the publication of our work in *Nature Communications*. We have revised this manuscript according to your professional comments and kind suggestions. The detailed corrections are given in the revised manuscript and highlighted in yellow color. The detailed revisions are listed below:

Reviewer #1 (Remarks to the Author):

In this manuscript, Bi and co-workers describe a Ciamician-Dennstedt reaction using α-halogen-free carbenes as the carbon source, converting indoles/pyrroles into structurally diverse quinoline/pyridine scaffolds. This method allows the introduction of fluoroalkyl, aryl, heteroaryl, alkenyl, alkynyl, and alkyl groups. The synthesis of several medicinally bioactive quinolines demonstrates the utility of their protocol. Control experiments and DFT calculation results indicate that the crucial 1,4-dihydroquinoline intermediate can undergo different pathways to yield various insertion products, depending on the carbene precursor and reaction conditions.

The authors propose the use of α-halogen-free carbenes. A recent work by Glorius (Nat Catal, 2024, 7, 242–251) used α-iodonium diazo compounds with various functional groups as the carbon source for ring expansion. However, the carbene reagent in this study is simpler, and their previous work (Angew. Chem. Int. Ed, 2024, 63, e202313807) has enhanced the practicality of the agent. Compared to previous studies, although this work employs more complex and stringent reaction conditions, it enables the introduction of a broader range of functional groups.

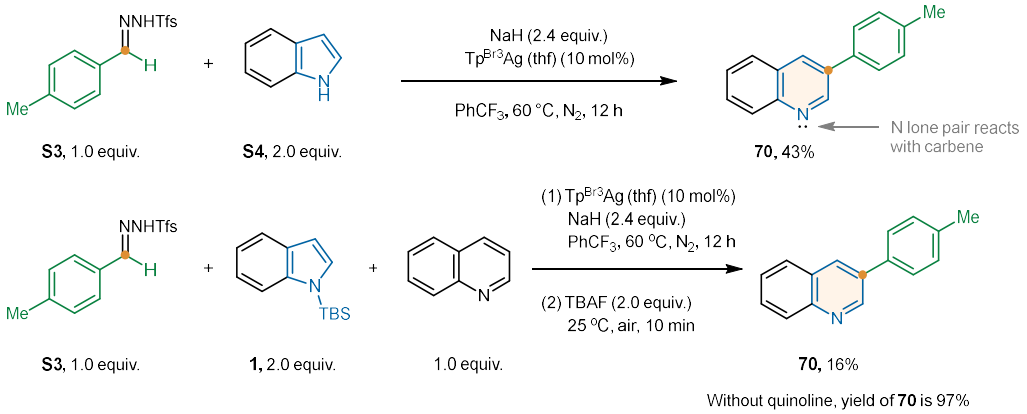
In my opinion, the chemistry reported is interesting and suitable for publication in Nature Communications following minor revisions:

Response: We thank the reviewer for the positive comments on our work and the valuable suggestions. We will address each specific concern below.

Q1: a) The manuscript employs N-TBS-protected indoles as substrates. How does the transformation perform with NH-indoles? Does it fail in these cases?

Response: Thank you for your professional comments. The reaction of NH-indoles with *N*-triftosylhydrazones generally produced the one-carbon insertion products in much lower yields. This is probably due to the fact that the initially formed quinoline derivative can subsequently react with a carbene to form an *N*-ylide, consuming both the carbene and the desired product while greatly reducing the reaction yield.

For example, the reaction of NH-indole **S4** with *N*-triftosylhydrazone **S3** afforded the one-carbon insertion product **70** in 43% yield (please see entry 17, Supplementary Table 6). The addition of 1 equiv. of quinoline to the reaction of *N*-TBS indole **1** with *N*-triftosylhydrazone **S3** afforded **70** in 16% yield, compared to 97% yield in its absence. This result is consistent with those reported in the literature (Levin, M. D. et al. *J. Am. Chem. Soc.* **2021**, *143*, 11337 and Ball, L. T. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202305081). Therefore, the facile generation of cyclopropane intermediate in high yield from the reaction of *N*-TBS indoles with metal carbenes is critical to the success of this transformation.



Q2: The *N*-TBS-protected pyrroles do not yield the target products with copper(I) catalyst, yet the reaction of 1*H*-pyrrole works using $Rh_2(esp)_2$ as a catalyst. Please explain why.

Response: Thank you for the valuable suggestions. In response to this comment, we investigated the reaction of *N*-TBS-substituted pyrrole **S8** with *N*-triftosylhydrazone **S10** (entries 1-3, Supplementary Table 7). The catalysts tested ($Tp^{Br3}Cu$ (CH_3CN), $Tp^{Br3}Ag$ (thf) and $Rh_2(esp)_2$) did not yield the desired one-carbon insertion product **119**, instead giving a mixture of carbene dimers as the main product along with < 20% of C–H insertion product. This result is consistent with the previous experimental observations that the chemoselectivity of the reaction of pyrroles with carbenes is highly dependent on the *N*-substituent: electron-withdrawing groups favor C=C cyclopropanation, whereas electron-donating groups give rise to

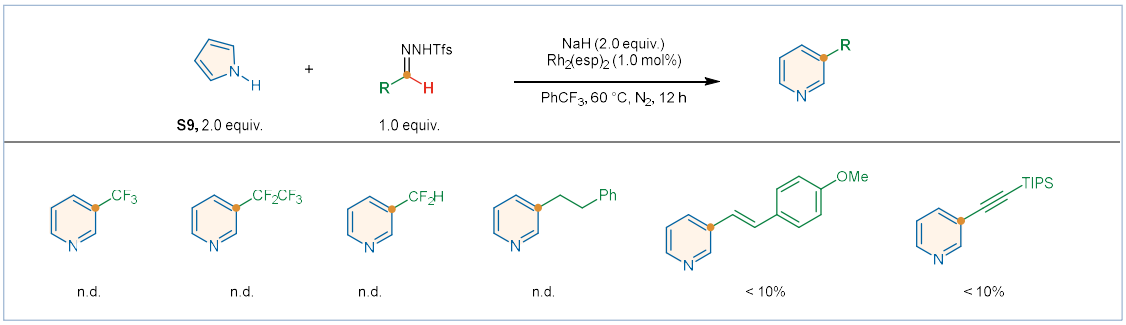
C–H insertion products (Díaz-Requejo, M. M. & Pérez, P. J. et al. *Adv. Synth. Catal.* **2020**, *362*, 1998). Inspired by the work of Pérez and coworkers, we turned our attention to 1*H*-pyrrole and found that 1*H*-pyrrole **S9** could afford the carbon insertion product **119** in 48% yield when using $Rh_2(esp)_2$) as catalyst (entry 6, Supplementary Table 7).

An explanation has been added in the revised main text, as follows: "Unfortunately, under similar conditions, *N*-TBS-protected pyrrole failed to afford the desired ring-expansion product (entries 1-3, Supplementary Table 7), which is consistent with previous observations that C–H insertion is favored over C=C cyclopropanation when electron-donating group-protected pyrroles react with copper or silver carbene [49]. Inspired by the work of the Levin group, we turned our attention to 1*H*-pyrrole and were delighted to find that 1*H*-pyrrole could afford carbon insertion product **119** in 48% yield when using $Rh_2(esp)_2$ as a catalyst (Supplementary Table 7)."

Q3: c) The manuscript does not report the reaction of *N*-triftosylhydrazones other than aryl *N*-triftosylhydrazones (e.g., trifluoroacetaldehyde *N*-triftosylhydrazone, pentafluoroethyl *N*-triftosylhydrazone, and alkyl, alkene, alkyne *N*-triftosylhydrazone) for 1*H*-pyrrole. How do these transformations perform? More clarity on these omissions and on reaction limitations, in general, would be appreciated.

Response: Many thanks for the helpful comments and suggestions. Other types of *N*-triftosylhydrazones, such as trifluoromethyl-, perfluoroalkyl-, alkyl-, alkenyl- and alkynyl-substituted *N*-triftosylhydrazones, failed to react with 1*H*-pyrrole to deliver the corresponding one-carbon insertion products. We have added the following descriptions to describe this limitation in the revised manuscript.

"Unfortunately, other types of *N*-triftosylhydrazones, such as trifluoromethyl-, perfluoroalkyl-, alkyl-, alkenyl- and alkynyl-substituted *N*-triftosylhydrazones, are not suitable carbene precursors, representing a current limitation of the reaction (Supplementary Fig. 2)."



Supplementary Fig. 2. The unsuccessful reaction for one-carbon insertion of 1*H*-pyrrole.

Q4: d) In Fig. 5a, the condition for step 2 is incorrect; it should be 25 °C for 10 minutes. Corrections are also needed in the Supporting Information. In Fig. 2b, what does "R_f = F" mean? Is it CF_3? This is not clear. Please verify this and ensure the manuscript is free from similar mistakes.

Response: Thank you for pointing out these errors. The errors in Fig. 5a have been corrected as follows:

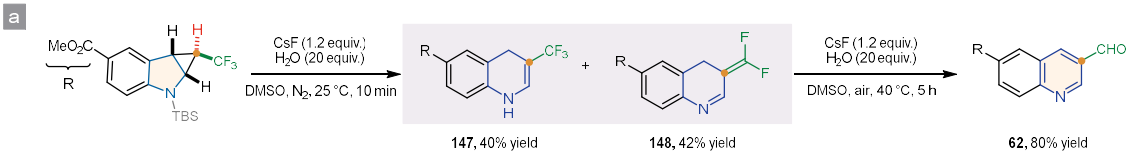
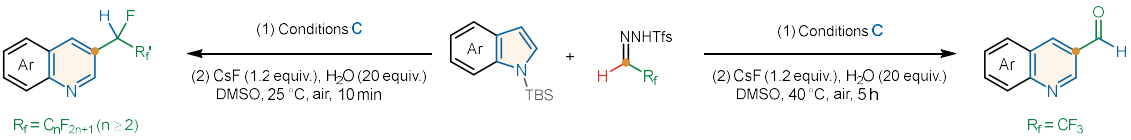


Fig. 5. Mechanistic studies of carbon-atom insertion of indoles with fluoroalkyl carbenes. a, Identification of the reaction intermediates.

The following modifications have been made in the revised manuscript: "Second, we were able to isolate trifluoromethyl cyclopropane **146** as a single diastereomer from the reaction of ester-substituted indole with TFHZ-Tfs (**2**) (Supplementary Fig. 6)."

The mistakes in Fig. 2b have been corrected as follows:



The reaction conditions C have been added in the footnote of Fig. 2.

Reviewer #2 (Remarks to the Author):

Bi and co-workers report the ring expansion of *N*-silyl indoles to 3-functionalized quinolines. This is a very useful addition to the growing field of 'molecular editing' (Ciamician-Dennstedt) methods that have been reported recently, because it expands the scope of groups that be inserted from Ar (Bonge-Hansen, Levin, Ball) or halogen to include fluoroalkyl, vinyl, and formyl. The reaction also exhibits high FG compatibility, which for the arylative ring expansion surpasses the scope of the methods from Levin and Ball. The method is likely to be of broad interest to the synthetic community.

Response: We thank the reviewer for the positive comments on our work and constructive suggestions. These comments and suggestions have helped us further improved the quality of our work. We will address specific concerns below.

COMMENTS:

The introduction needs to be more balanced to avoid appearing misleading/disingenuous. For example, the use of metal carbenoids to effect ring expansion was reported by Bonge-Hansen, but this work is not discussed appropriately (instead it is thrown in to the general discussion of halocarbenes, which are not implicated in their work). Also, Bi et al have previously used the same strategy (and very similar reaction conditions) with ketone-derived Tfs-hydrazones to effect ring expansion of indoles; the only difference in the present paper is that an aldehyde-derived hydrazone allows for oxidation of the ring expansion product to a quinoline. Rather than trying to inflate the novelty of the present work (see also the comments on Fig 4), the authors should focus on fully explaining the practical benefits, which include the scope:

Q1: Throughout the scope (and especially in the discussion of the arylative expansion), the authors could really highlight the value of their work by discussing where it goes beyond the current state of the art defined by Levin and Ball. For example, Levin and Ball's chemistry isn't demonstrated for basic N (eg, azaindoles), aldehydes, acidic protons (eg, alcohols), alkenes, epoxides, vinylative expansions… This is a missed opportunity to really highlight the benefits of the present work that I encourage the authors to embrace.

Response: Many thanks for the helpful comments and suggestions. As per the suggestions, we have

re-draw Fig. 1 as follows:

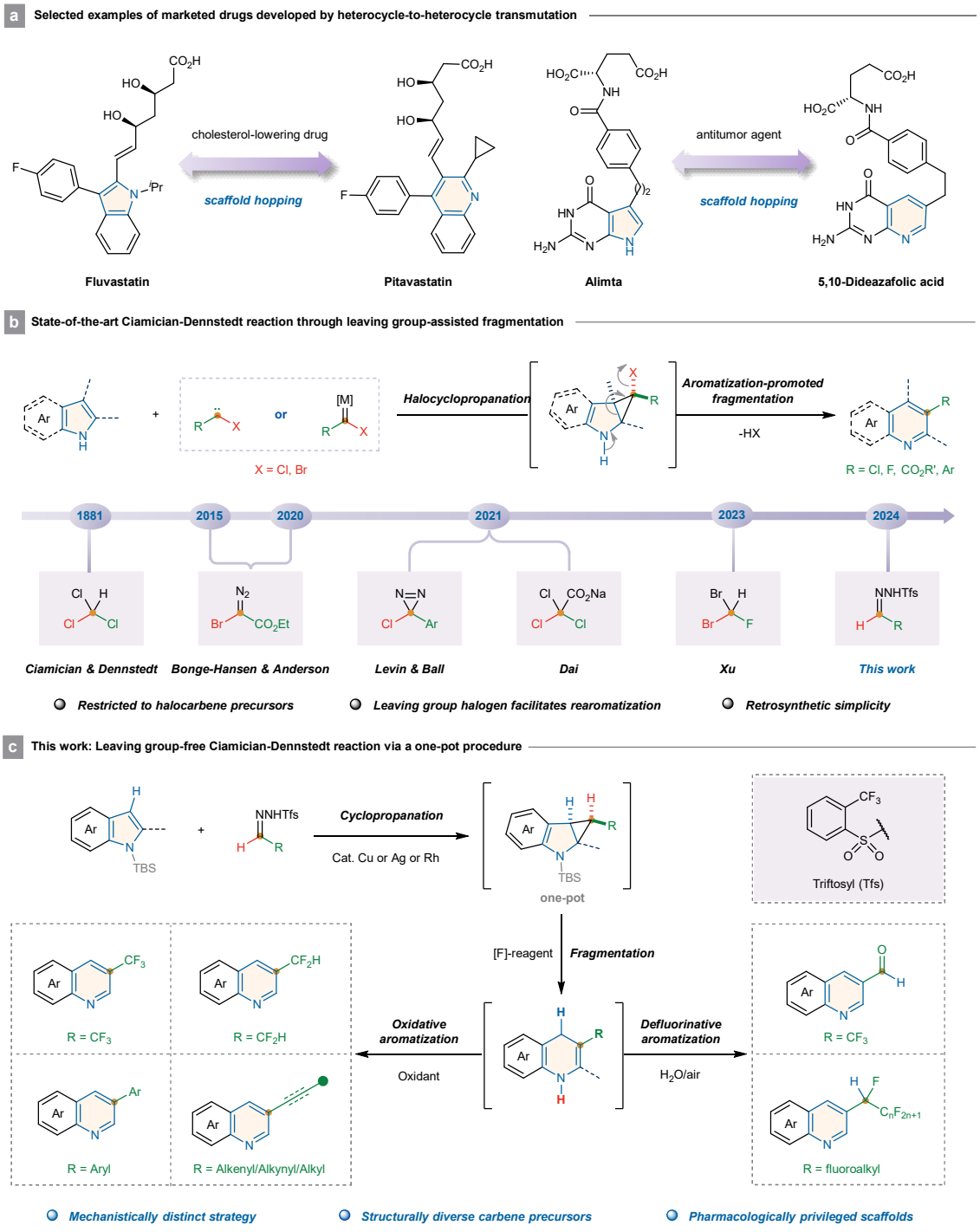


Fig. 1. Ciamician-Dennstedt rearrangement reaction: background and development.

As per the suggestion, we have made the following changes in the Abstract: "This one-pot,

two-step protocol enables the insertion of various carbenes, including those previously unexplored in C-D skeletal editing chemistry, into indoles/pyrroles scaffolds to access 3-functionalized quinolines/pyridines."

The following changes in the Introduction: "In recent years, Levin, Ball, Xu and others have made significant contributions to the evolution of this chemistry[30–36]. To date, the C-D reactions have been achieved through free carbenes generated from thermally- or photo-activated halocarbene sources (e.g. chloroform[28], CCl_3CO_2Na[29], α-chlorodiazirines[30,31], dibromofluoromethanes[31,32]) and metal carbenes by rhodium- and enzyme-catalyzed decomposition of α-halodiazoacetates[34-36]."

"Very recently, we have developed a couple of skeletal editing of *N*-heteroarenes through dearomative carbon atom insertion, accessing *N*-heterocycles bearing a quaternary carbon center by trapping of a disubstituted carbenes generated from fluoroalkyl *N*-triftosylhydrazones[25,38,39]. We wondered whether this strategy would be applicable in Ciamician-Dennstedt reactions using leaving group-free carbenes; if successful, would considerably expande accessible chemical space of this skeletal editing technique, especially late-stage editing of complex molecules."

The following changes in reaction scope investigation: "We could further expand the scope of *N*-triftosylhydrazone substituents to alkyl, alkene, and even alkyne groups; these insertions also proceeded smoothly, producing the corresponding 3-alkyl-, alkenyl-, and alkynyl-quinolines (**87**–**92**) in good to excellent yields, which were challenging to access with previous approaches using α-chlorodiazirines as one-carbon source[30,31]."

"In addition, 7-azaindole and 5-chloro-7-azaindole, which had not previously been demonstrated[30-36], produced the corresponding ring expansion products (**109** and **110**)."

The following changes in Conclusion: "In summary, this study substantially expands the chemical space of Ciamician-Dennstedt reaction by using functionalized *N*-triftosylhydrazones as carbene precursors. This one-pot, two-step procedure allows a variety of carbenes to be inserted into the skeletons of indoles and pyrroles, accessing the corresponding quinolines and pyridines with various 3-substituents, such as trifluoromethyl, difluoromethyl, fluoroalkyl, formyl, alkyl, alkenyl, alkynyl, aryl and heteroaryl, most of which are challenging to be installed with existing C-D skeletal editing technique. "

Q2: Please discuss the thermal stability of the hydrazones in the manuscript, and re-state any issues in the SI.

Response: Many thanks for the valuable comments and suggestions. As per the suggestion, we conducted a thermal hazard assessment of trifluoromethyl and phenyl-substituted *N*-triftosylhydrazones using differential scanning calorimetry (DSC). The results suggest that there was no impact sensitivity (IS) and/or explosive propagation (EP) in *N*-triftosylhydrazones. These results were added to Supplementary Information.

The following sentences have been added to the main text: "Thermal hazard assessment using differential scanning calorimetry (DSC) suggested that there was no impact sensitivity (IS) and/or explosive propagation (EP) in *N*-triftosylhydrazones (Supplementary Table 8 and Supplementary Figs. 3 and 4), further confiming that *N*-triftosylhydrazones are operationally safe compared to the corresponding diazo compounds[40]".

The following statement has been added to Supplementary Information, please see page S1: "The differential scanning calorimetry (DSC) shows that *N*-triftosylhydrazones do not exhibit impact sensitivity (IS) and/or explosive propagation (EP). Although we found no energetic decomposition in our work with *N*-triftosylhydrazones, caution should be taken in handling large quantities of *N*-triftosylhydrazones, because the diazo compounds generated from *N*-triftosylhydrazones are high-energy compounds."

Q3: Show the structure of the ligand at its first mention in the manuscript (eg, fig 1).

Response: Thanks for the professional suggestion. We have added the structure of ligand Tp^{Br3} in Fig 2a and defined catalyst "$Rh_2(esp)_2$" as "Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)" in the footnote of Fig. 3.

Q4: Show the structure of Tfs at its first mention in the manuscript.

Response: Thanks for the professional advice. We have added the structure of Tfs in Fig. 1c and defined "Tfs" as "triftosyl" in the footnote of Fig. 1.

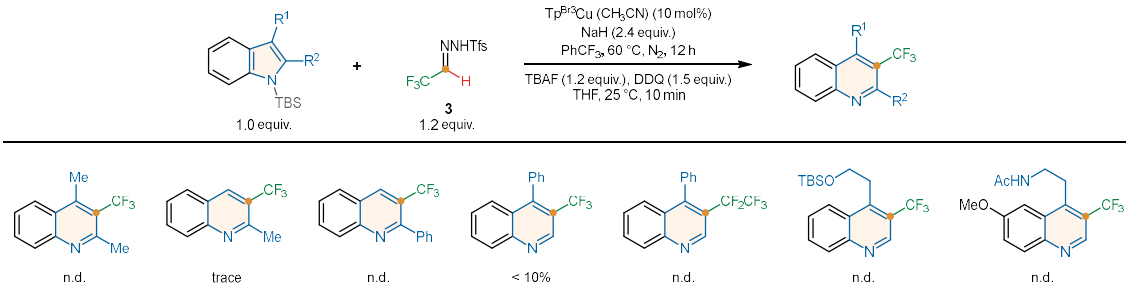
Q5: P5, L105: the claim that amine functional groups are tolerated is inaccurate; cpd 13 is a Boc-amine.

The text should be changed to state "…protected amine (13)" or similar.

Response: Thank you for pointing it out. We have revised it as suggested.

Q6: P5, L109: It is good that the limitations of the scope are noted ("3-methyl-TBS-indole produced ring expansion product **4** in ~20% yield."). However, it would be useful if the authors could comment on whether the failure of 3-substituted indoles in the fluoroalkylation is general (ie, are other 3-substituents tolerated under the conditions of Fig 2?). The authors should also state explicitly whether (a) 2-substituted indoles are tolerated in the fluoroalkylative ring expansion, and (b) whether pyrroles are compatible with the fluoroalkylative ring expansion (they are demonstrated only for the arylative expansion).

Response: Thank you for the helpful comments and suggestions. In response to the suggestions, we have prepared and tested various 3- and 2-substituted indoles using the standard reaction conditions. The results are summarized in Supplementary Fig. 1.

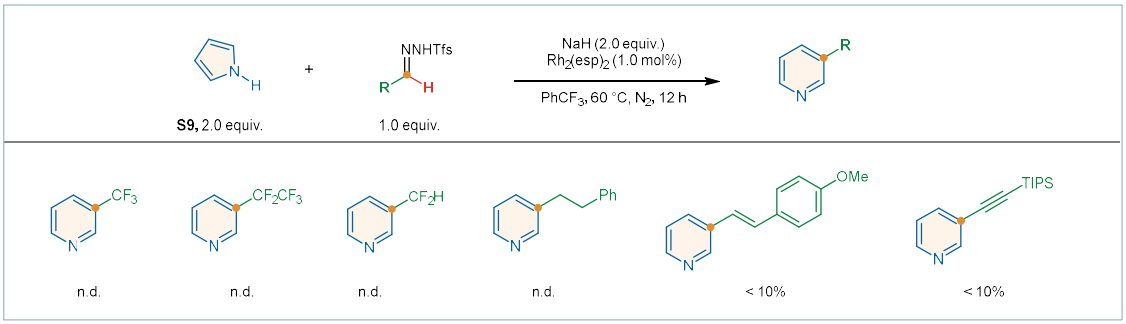


Supplementary Fig. 1. The unsuccessful examples of ring expansion of indoles with fluoroalkyl *N*-triftosylhydrazones.

We have added the following sentences to the revised manuscript: "For example, the sterically hindered 3-methyl or 3-phenyl TBS-indole displayed much lower yield (i.e., 20% for product **4**), and no ring-expansion products were observed when subjecting 2-substituted indoles to the standard reaction conditions (Supplementary Fig. 1)."

In fact, we have tested many other types of *N*-triftosylhydrazones but no desired ring-expansion product were detected for trifluoromethyl-, perfluoroalkyl-, alkyl-, alkenyl- and alkynyl-substituted *N*-triftosylhydrazones. The results are summarized in Supplementary Fig. 1 and the following comments have been added to the revised manuscript: "Unfortunately, other types of *N*-triftosylhydrazones, such as

trifluoromethyl-, perfluoroalkyl-, alkyl-, alkenyl- and alkynyl-substituted *N*-triftosylhydrazones, are not suitable carbene precursors, representing a current limitation of the reaction (Supplementary Fig. 2)..”



Supplementary Fig. 2. The unsuccessful examples one-carbon insertion of 1*H*-pyrrole.

Q7: P7, L163: “…and pyridine substituents all successfully introduced in high yields”. The pyridyl unit is inserted in 35%, which is not a high yield. Please adjust the text accordingly.

Response: Thank you for pointing it out. As suggested, we have removed “in high yields” from the above-mentioned description .

Q8: Fig 3: For cpd 106, please add a footnote to state that the SM was a doubly-TBS protected indol, and that the silyl ether is deprotected under the reaction conditions. Don’t leave this detail only in the body text.

Response: Many thanks for the helpful suggestion. As suggested by reviewer’s, we have added the following footnote for compounds **75**, **98**, **108** and **111**: “The OH group in indole or *N*-triftosylhydrazone was protected by TBS and deprotected in the reaction conditions.”

Q9: P7, L183: The authors could/should mention that tryptophol and melatonin are 3-substituted indoles, which is a motif not tolerated in the fluoroalkylative expansion.

Response: Many thanks for your valuable suggestion. As per the suggestion, we have added the following text to the revised manuscript: “Notably, the sterically hindered 2- and 3-substituted indoles that are not amenable to the fluoroalkylative expansion, have undergone arylative ring expansion with synthetically meaningful yields (e.g., **107**, **108**, **111** and **112**).”

Q10: P7, L197: “A brief survey of pyrrole scope revealed that 2-(trichloroacetyl)-1*H*-pyrrole provided the

desired pyridine **126** in 59% yield, …" fig 3 shows cpd 126 as dichloroacetyl. Please check.

Response: Many thanks for your comments. We have carefully checked the structures of the starting material and product by NMR and HRMS. A chlorine in the product was protonated for an unknown reason. In order to avoid confusion, we have modified the text as follows: "A brief survey of the pyrrole scope revealed that 2-(trichloroacetyl)-1*H*-pyrrole provided 2-(dichloroacetyl)pyridine **126** in 59% yield"

Q11: Fig 4: This figure is misleading. By drawing unfair comparisons between literature methods and the present method, it over exaggerates the relative benefit of the ring expansion (RE) chemistry. The literature methods are all shown going back to very simple commercial building blocks, resulting in high step counts and low yields. For example, for the first panel, the literature routes go through 3-bromoquinolin-7-ol, which is commercially available (but expensive). If you instead report the literature routes from this intermediate they are one step, and the yield of cpd 131 beats that of the ring expansion approach. Similarly, the ring expansion route does not account for preparation of the TBS-indoles (some are commercial/custom synthesis, but are very expensive), the hydrazone, the hydrazide, the ligand, or the catalyst. This figure (and associated discussion/SI) must be amended to give a fairer comparison, based on starting materials of similar complexity and accounting for the synthesis of all necessary reagents or catalysts that are not commercial (and again, apply the same standards to what you consider 'commercial').

Response: Many thanks for your comments and professional suggestions. We agree with the reviewer that Fig.4 and the descriptions are misleading. As per the suggestion, we have re-drawn the Fig. 6 and modified the text as follows: "One advantage of this protocol is that OTBS-substituted indoles could directly provide OH-containing quinoline derivatives. Taking advantage of this, we successfully synthesized potential anticancer agents[50] **131** and **132** from commercially available indole **129** in two steps with 72% and 49% total yields, respectively (Fig. 4a). This protocol has better tolerance for arylcarbenes with strong electron-donating groups compared to previous protocols using α-chlorodiazirines as the one-carbon source[30,31]. For example, 3-(4-methoxyphenyl)quinoline-2-carbaldehyde **134**, a key intermediary for the synthesis of pharmaceuticals with antiproliferative (**136)** and anti-dengue activity (**137**), can be obtained in two steps from 2-methylindole **134** with an overall yield of 62% (Fig. 4b). Notably, the compound **134** was previously prepared from isatin **136** in three steps, with 53% overall yield[51]. Applying this silver-catalyzed

C-D protocol, electron-rich aryl-substituted quinoline derivatives **138**, **140** and **142** can be obtained in 90%, 81% and 89% yields, respectively. These compounds can be further transformed into bioactive molecules, such as anti-inflammatory compound **139**[52], β-glucuronidase inhibitor **141**[53] and antimycobacterial treatment adjuvant **143**[54], in two steps with preparatively useful total yields (Fig. 4c). Finally, the Buchwald-Hartwig amination of product **144**, which was obtained by one-carbon insertion in 88% yield, with morpholine afforded quinoline **145** in 80% yield, which is used for the treatment of hypopharyngeal cancer[55]"

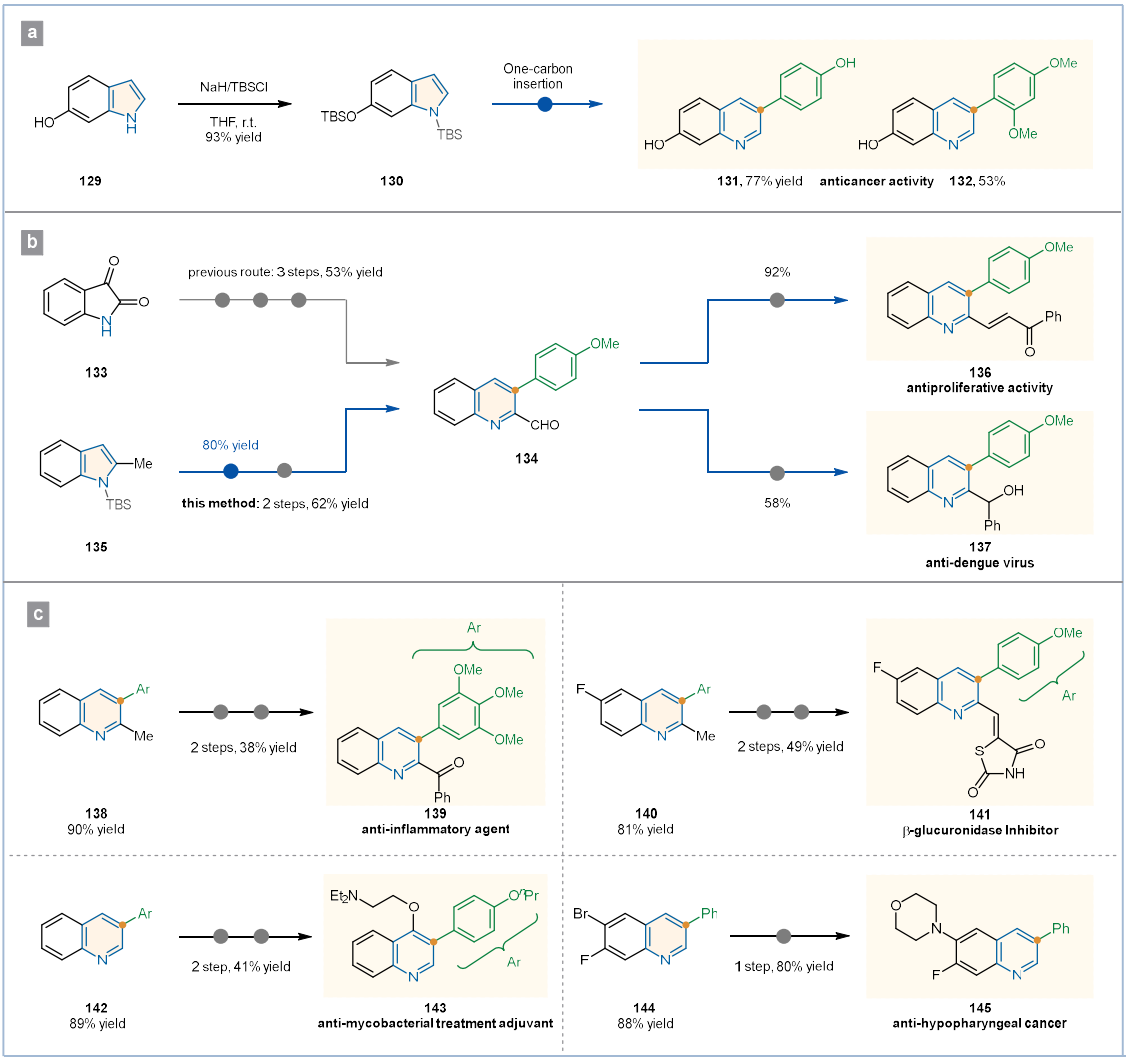


Fig. 4. The synthetic utility of the halogencarbene-free Ciamician-Dennstedt reaction in total synthesis of bioactive molecules.

Q12: P9, L247: "indicating a kinetic isotope effect (k_H/k_D) of 3:1… and appear to suggest an internal 1,3-hydride shift, which may be the rate-determining step of the reaction." First, the observed KIE cannot be used to draw conclusions on the RDS of the reaction. The KIE has been measured from an intramolecular competition, so in isolation it can only be used to draw conclusions about a selectivity determining step. Please amend the discussion appropriately. Second, there is no strong evidence (from the experiments shown in Fig 5b) that the H transfer is "internal" (presumably 'intramolecular'?): the use of ^{1}H NMR to measure distribution of D in cpd 56-d (reaction 2 in panel b) tells us the overall position of the D (ie, whether it is on the quinoline or in the formyl group), but not whether D has been transferred between molecules (ie, some molecules may have D at both positions, other molecules may have no D; the overall quinoline:formyl distribution is unchanged). This analysis can be done by looking at the isotope distribution in the the HRMS data (which is not presented in the SI) and correcting for 13C isotopomers. The outcome of this analysis should be presented in the manuscript to support either an inter- or an intramolecular H transfer.

Response: Many thanks for your comments and professional suggestions. We apologized for using the intramolecular competition to draw conclusions on the RDS of the reaction. We attempted to determine the KIE of two parallel reactions, but we unable to obtain the pure **147-*d*$_2$** with high level of deuterium-incorporation. The reproducibility of the KIE determined from two parallel reactions is poor when using the crude **147-*d*$_2$** with 65% deuterium-incorporation. In order to determine whether the H transfer is inter- or an intramolecular, a crossover experiment is performed (Fig. 5b). The cross-over experiment of deuterated **147-*d*$_2$** and non-deuterated **149** afforded bis-deuterated compound **62-*d*** and non-deuterated **56-*d***, indicating that the aldehyde hydrogen in **56** may derive from the C4-H of the 1,4-dihydroquinoline intermediate, and proceed through a formal intramolecular 1,3-hydrogen shift.

We have re-drawn the Fig. 5a and 5b as follows:

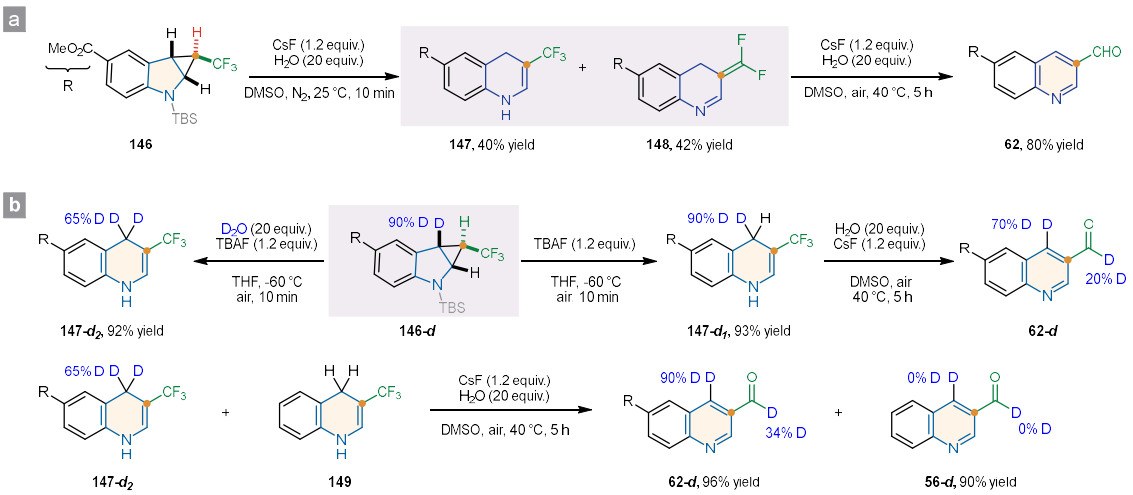


Fig. 5. Experimental sudies and proposed mechanism for carbon-atom insertion of indoles with fluoroalkyl carbenes. a, Identification of the reaction intermediates. **b,** Experiments to probe the source of the hydrogen atom incorporated in quinoline-3-carboxaldehyde.

According to the new Fig. 5, we have modified the text as follows: "Treatment of the deuterated cyclopropane **146-*d*** with TBAF at -60 °C for 10 minutes resulted in the formation of the mono-deuterated 1,4-dihydroquinoline **147-d_1** (90% D incorporation), which was further converted into the deuterated product **62-*d*** with 20% D incorporation at the carbonyl carbon and 70% D retention at the C4-position. This result suggests that deuterium atoms in **146-d_1** are perfectly retained in **62-*d*** and hydrogen atoms transfer to carbonyl carbon preferentially over deuterium atoms. Bis-deuterated 1,4-dihydroquinoline **147-d_2** (65% D incorporation) was isolated in 92% yield by treating **146-*d*** with TBAF/D_2O at -60 °C for 10 minutes. The cross-over experiment of deuterated **147-d_2** and non-deuterated **149** afforded bis-deuterated compound **62-*d*** and non-deuterated **56-*d*** (Fig. 5b). Furthermore, D incorporation at carbonyl carbon was improved to 74% when using bis-deuterated 1,4-dihydroquinoline with 80% D incorporation (Supplementary Fig. 8). These results indicate that the aldehyde hydrogen in **56** may derive from the C4-H of the 1,4-dihydroquinoline intermediate, and proceed through a formal intramolecular 1,3-hydrogen shift.".

Q13: P9, L248: "… an internal 1,3-hydride shift". 1,3-hydride shifts require an antarafacial topology, so do not occur. From the computational results it seems that the H transfer is mediated by CsF and DMSO, so this process presumably cannot be considered a 'pure' 1,3-H shift. Please adjust the terminology used (eg,

to “a formal 1,3-hydride shift”) to avoid confusion.

Response: Many thanks for your professional suggestion. We agree with the reviewer and have changed the “1,3-H shift” to “formal 1,3-hydrogen shift” or “CsF/DMSO assisted formal 1,3-H transfer”.

Q14: Fig 5b: k_H/k_D, not K_H/K_D.

Response: Thank you for pointing it out. K_H/K_D in Fig. 5b has been removed from the revised manuscript.

Q15: P13, L353: “The methodology is general, straightforward, scalable…” This claim is questionable, and should be deleted: there are clear limitations to scope (eg, 2- or 3- substituted indoles in Fig 2) or FGs that are not tested (especially acidic/epimerizable groups), so it is not possible to claim generality. The ‘straightforward’ claim is not realistic because the reagents and catalysts have to be prepared. The ‘scalable’ claim is not realistic due to the use of NaH (gas evolution) and fluorinated solvents (EU PFAS regulations).

Response: Many thanks for your comments. We have removed this sentence from the conclusion.

Q16: Supp Info:

The authors should state how the following compounds were prepared (with characterization data & spectra), or where they were purchased from: silyl indoles / pyrroles, ligands, catalysts, Tfs hydrazide.

Response: This is a good suggestion. As suggested, we have added the experimental procedures, characterization data and NMR spectra or references for silyl indoles/pyrroles, ligands, catalysts and Tfs hydrazide to the Supplementary Information. Please refer to our revised Supplementary Information (Pages 9 to 22).

Reviewer #3 (Remarks to the Author):

In this manuscript, Bi, Anderson, Liu, and coworkers report a mechanistically distinct Ciamician-Dennsteadt (CD) reaction of indoles and pyrroles to access 3-functionalized quinolines and pyridines. Compared to reported approaches relying on halogenated carbenes, using functionalized N-triftosylhydrazones as carbene precursors enables a general platform for single-atom skeletal diversifications with numerous functionalities that were challenging to introduce with previous approaches. The reaction exhibits a broad substrate scope toward both components, with more than 130 3-functionalized quinolones synthesized. Moreover, access to 3-perfluoroalkylated quinolines as well as possible variations on carbene precursors make this method very general. The authors successfully applied this protocol for the total synthesis and late-stage skeletal modification of bioactive complex molecules, including drugs and natural products. It also provides experimental and theoretical evidence to support the proposed mechanism that proceeds via the formation of 1,4-dihydroquinoline intermediate and the origins of the chemoselectivity. Overall, the manuscript is well organized, the experiments conducted to a high standard, and the accompanying supporting information effectively supports the conclusion drawn in this study.

Since the single-atom skeletal editing of heteroarenes is a hot topic in current research, the findings reported here for the CD reaction of indoles and pyrroles using halogen-free carbene precursors deserve to be published in a high-ranking journal such as Nat. Commun. Hence, I strongly support its publication after addressing the following comments and suggestions.

Response: We thank the reviewer for supporting the publication of our work Nature Communications and for their constructive review comments.

There are some issues that the authors should address before the publication of this work.

Q1: The late-stage single-atom skeletal editing of raputimonoindole B is quite interesting. Did the authors notice any competing cyclopropanation or ring expansion products of furan on the raputimonoindole B molecule?

Response: Many thanks for your comments. In response to this comment, we reexamined the reaction of

Raputimonoindole B with CF_3- and Tol-substituted *N*-triftosylhydrazones, which afforded desired the one-carbon insertion product **23** and **113** in 84% and 37% yields, respectively. The careful analysis of the crude product obtained from Tol-substituted *N*-triftosylhydrazone indicated that the reaction mixture consisted of the desired product **113** (42% NMR yield), Raputimonoindole B (42% recovery) and carbene dimers as the major by-product. No competing cyclopropanation or ring expansion products of furan were observed in both reactions.

Q2: Some alkene and alkyne functionalities were tolerated in the optimized protocol. Did the authors observe any [2+1] cycloaddition side reactivity? It might be interesting to comment on this.

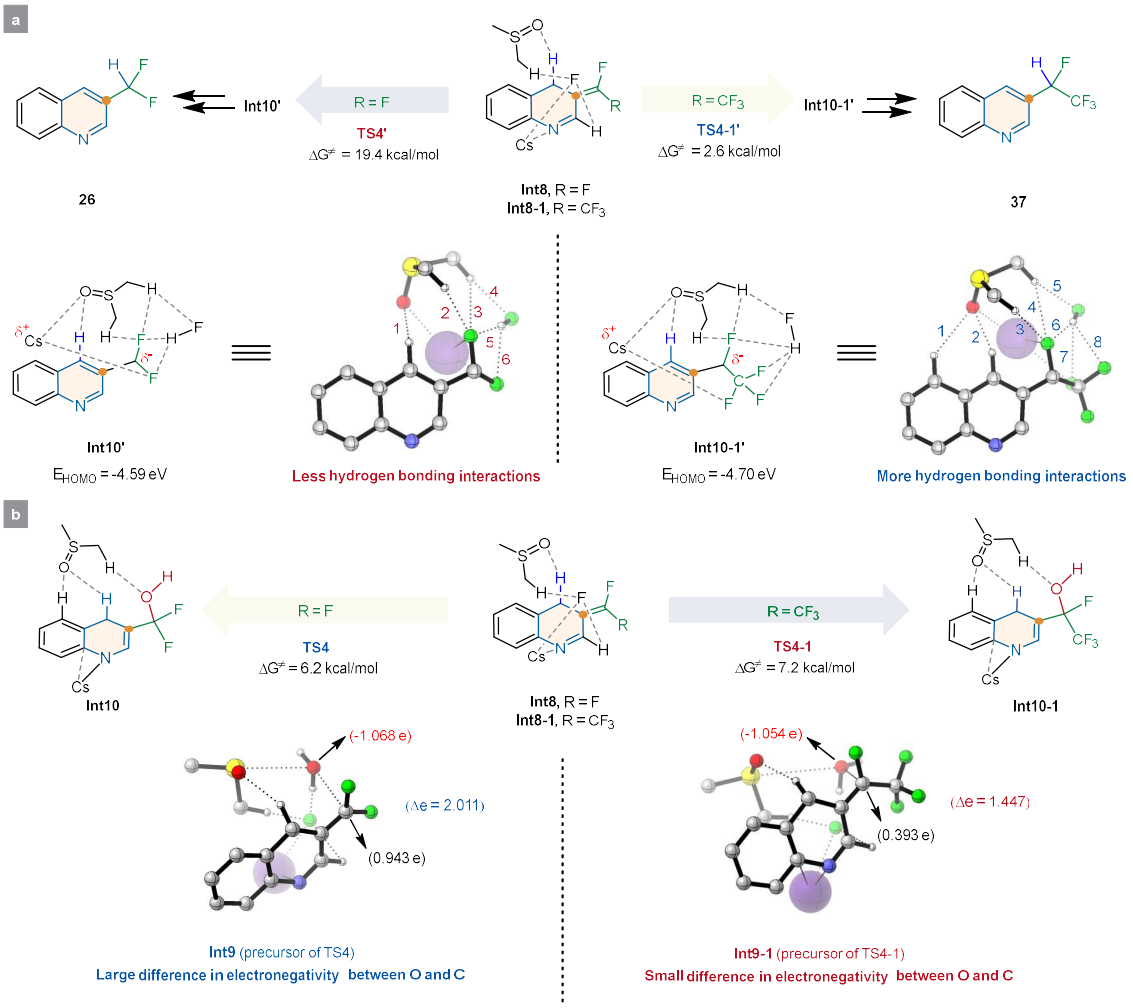
Response: Many thanks for your comments and professional suggestions. No side products arise from the competing [2+1] cycloaddition, N−H and C−H insertion reactions under the optimized catalytic reaction conditions. As suggested, we have added the following descriptions to the revised manuscript: "Overall, this fluoroalkylative ring expansion exhibits high chemoselectivity, with no competing [2+1] cycloaddition (**16**, **17**, **24**, **25** and **33**), N−H insertion (**13**) and benzylic or allylic C−H insertion (**20** and **30**) products found in the presence of copper carbene."

Q3: In supplementary Fig. S18B, the authors explain the difference in Michael addition reaction outcomes of the CF_3- and C_2F_5-substituted carbenes by comparing the electronegativity difference of O and C atoms in **TS4** and **TS4-1**. However, I think it is more reasonable to make a comparison between the corresponding intermediates.

Response: Thank you for your insightful comments. As per the suggestions, we have compared the electronegativity difference of O and C in corresponding intermediates **Int9** and **Int9-1**. The calculation suggested that the difference in electronegativity between O and C atoms in **Int9** ($\Delta e = 2.011$) is larger than that in **Int9-1** ($\Delta e = 1.447$). The tendency is consistent with the conclusion obtained by comparing the transition states **TS4** and **TS4-1**. We have modified descriptions in the revised manuscript: "The chemoselectivity of **Int8-1** generated from the C_2F_5-substituted carbene is opposite. **Int8-1** preferentially occurs the formal 1,3-H transfer leading to defluorinative product **37** (via **TS4-1'**, $\Delta G^{\ddagger} = 2.6$ kcal/mol) rather than the Michael addition reaction (via **TS4-1**: $\Delta G^{\ddagger} = 7.2$ kcal/mol) (Fig. 6c and Supplementary Fig. 22). **Int9** (precursor of **TS4**) has a larger electronegativity difference between O and C atoms than **Int9-1** (the precursor of **TS4-1**) ($\Delta e = 2.011$ vs. $\Delta e = 1.447$, Supplementary Fig. 19b), thus lowering the energy

barrier of **TS4**. The large difference in electronegativity can be attributed to the stronger electron-withdrawing effect of the trifluoromethyl group than the fluorine atom, which is the origin of the reversed chemoselectivity of **Int8-1**."

We have also updated Supplementary Fig. 19 in the revised Supplementary Information as follows:



Supplementary Fig. 19. a, Comparision of CsF/DMSO-assisted formal 1,3-H transfer between CF_3- and CF_2CF_3-substituted carbenes**.** The allyl carbon anion intermediate **Int10'** generated from CF_3-substituted carbene is less stable compared with **Int10-1'** generated from CF_2CF_3-substituted carbene. This is owing to the strong electron-withdrawing effect of the trifluoromethyl group as well as the more and stronger hydrogen-bonding interactions in **Int10-1'**. **b**, Comparison of Michael addition between CF_3- and CF_2CF_3-substituted carbenes. The difference in electronegativity between O and C atoms in **Int9** (Δe = 2.011), which is the precursor of **TS4**, is larger than that in **Int9-1** (Δe = 1.447), resulting in that the energy barrier for **TS4** is lower than that for **TS4-1**. Values in e represent NPA charges. Most hydrogen atoms in 3D structures are omitted for clarity.

Q4: The authors need to check the structural formula of intermediate **148-d_1** in Fig. 5b. It should be a H/D ligated to the N atom rather than a methyl group. In Figure 6a, the F atom is not shown in the structures of intermediate **Int3** and transition state **TS2**. The authors should double-check the corresponding structure. Moreover, when DMSO was added to the free energy profile, the hydrogen bond between S and H was shown using dashed lines. However, I feel the O-H bond is more favored in this case. Have the authors considered the hydrogen bonding interaction between the O atom of DMSO and the H atom of the C-H bond?

Response: We thank the reviewer for their professional suggestions. Firstly, the structural formula of intermediate **148-d_1** errors in Fig. 5b have been corrected, please see Fig. 5b in our revised manuscript. Secondly, we have also added F atoms in the structures of **Int3** and transition state **TS2** in Figure 6a. Finally, we have performed the DFT calculation considering the coordination environment of Cs^+ in solvent DMSO and searched for the transition states **TS1** and **TS2** as suggested by the reviewer.

We have modified descriptions in the revised manuscript: "In addition, frontier molecular orbital (FMO) analysis indicates that the energy barrier for the 1,3-H transfer may be influenced by the energy of HOMO orbital and hydrogen bonding interactions in the formed allyl carbon anion intermediates. More specifically, the energy of HOMO orbital of **Int10'** leading to product **26** by CsF/DMSO assisted formal 1,3-H transfer of **Int8**, is higher than that of **Int10-1'** leading to product **37** (E_{HOMO} = -4.70 eV *vs*. E_{HOMO} = -4.59 eV). Besides, there are more hydrogen bonding interactions in **Int10-1'** (Supplementary Fig. 19a). All these factors can stabilize **Int10-1'** and make **Int-1** easier to occur CsF/DMSO-assisted formal 1,3-H transfer to give hydrodefluorination insertion product **37**."

The energies and structures of **Int2**, **TS1**, **Int3**, **Int4** and **TS2** in Fig. 6 have been updated as follows:

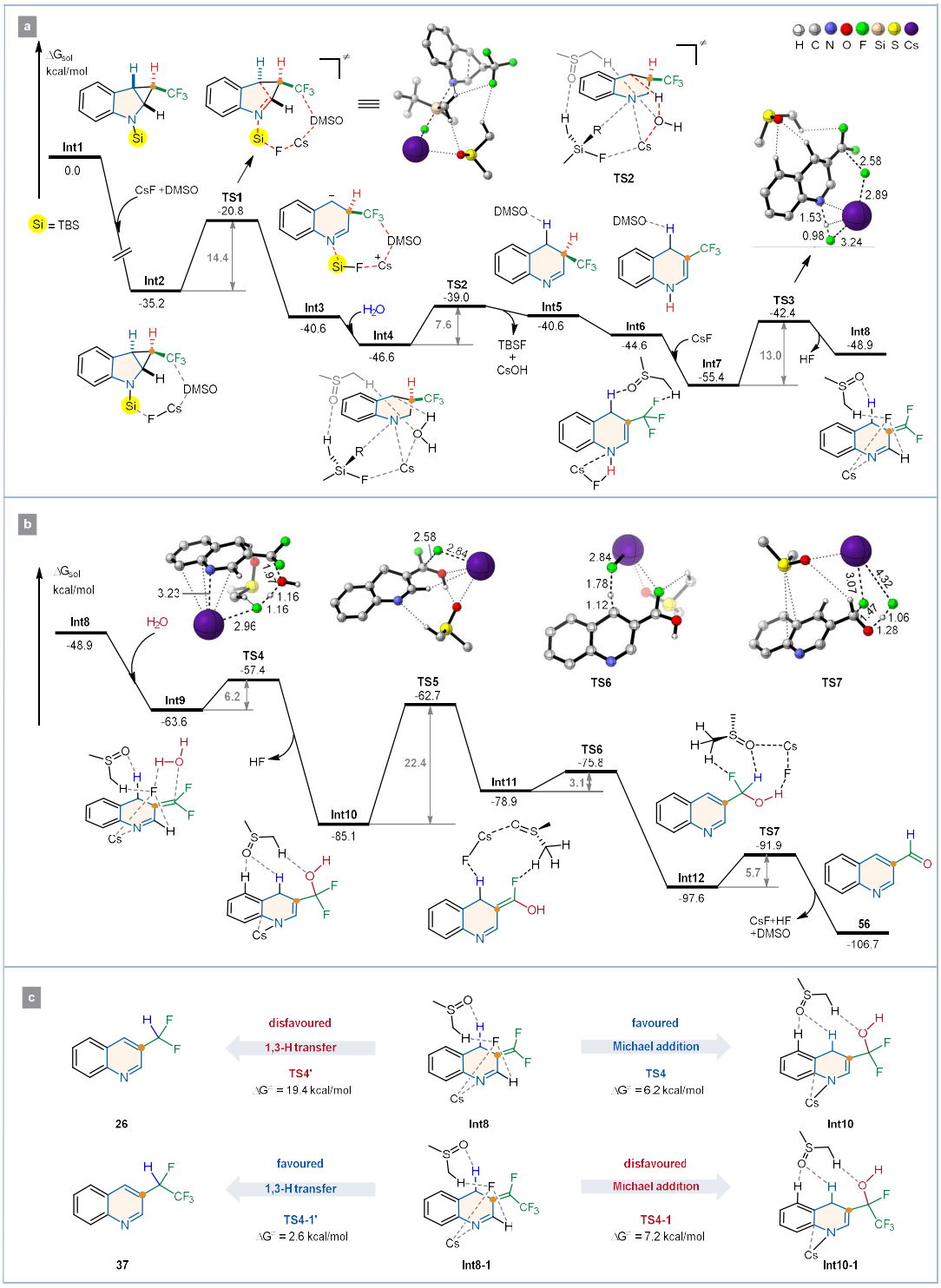
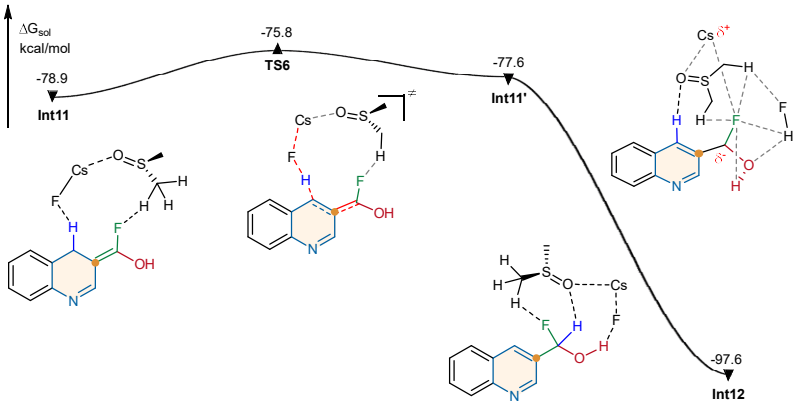


Fig. 6. Computational studies. a, Calculation of *gem*-difluoromethylene intermediate **Int8** formation. **b**, Calculation of Michael addition and CsF/DMSO assisted formal 1,3-H transfer of intermediate **Int8** leading to quinoline-3-carboxaldehyde **56**. **c**, Investigations into the origin of chemoselectivity between CF_3- and CF_2CF_3-substituted carbenes.

Moreover, we have searched the transition state **TS6** for the H-transfer process. Our calculations

suggest that the enol intermediate **Int11** first undergoes a concerted CsF/DMSO-assisted H-abstraction and tautomerization to form allyl carbon anion intermediate I**nt11'**, which then protonated with HF-DMSO-Cs adduct to give **Int12**. These results were updated in the revised manuscript **Fig. 6b** and supplementary **Fig. 20.**



Supplementary Fig. 20. The CsF/DMSO-assisted formal 1,3-H transfer of enol intermediate **Int11**. Allyl carbon anion intermediate **Int11'** was first formed with an energy barrier of 3.1 kcal/mol, followed by protonation with HF-DMSO-Cs adduct to give **Int12** instantly.

Reviewer #4 (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.

Response: Thanks very much for reviewing our manuscript and your kind support for the publication of our work in Nature Communications.

Finally, we would like to show our great respect to all Reviewers, whose critical reviews and invaluable suggestions have improved the quality of this manuscript. We hope that the revised manuscript will reach the level of publication in *Nature Communications*.

Thank you once again. We are looking forward to hearing from you.

Sincerely yours,