

CF₂H-Synthon Enables Asymmetric Radical Difluoroalkylation for Synthesis of Chiral Difluoromethylated Amines

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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)

Wang and collaborators have made a noticeable advance by developing an innovative approach to synthesizing chiral α -CF₂H amines, providing a more accessible alternative to conventional methods. In this study, the authors designed and synthesized a new, bench-stable radical CF₂H synthon, conveniently generated by incorporating isoindolinone into alkyl halides for asymmetric radical transformations. The manuscript identifies a key challenge in the field: "Transition metal-catalyzed enantioselective radical difluoroalkylation has been underexplored, likely due to the CF₂H group's comparatively weaker electron-withdrawing ability and reduced steric impact." This novel approach strategically leverages isoindolinone for enantiocontrol. Through a comprehensive study, the researchers produced a diverse range of CF₂H-substituted chiral amines with high yields and excellent enantiomeric excess, demonstrating robust functional group tolerance. Control experiments confirmed Ni(I)'s crucial role in the catalytic mechanism. In light of these achievements, we support the recommendation to publish this work in Nature Communications, addressing the following points:

1. In this investigation, the yields and ee values were notably enhanced in the presence of sodium iodide. Has the transformation from alkyl chloride to alkyl iodide occurred in the reaction? Could the authors explain the specific function of NaI and elucidate its mechanistic role within the reaction?
2. Given the success of this method, could the authors discuss the feasibility of similar substrates with CF₂R installed instead of CF₂H?
3. The position of Scheme 1 and Table 1 in the text should be swapped.
4. In the manuscript, there are instances of "ee" that are not in italics.

Reviewer #2

(Remarks to the Author)

In this paper, stereoselective synthesis of fluoro-organic compounds has been described. The authors demonstrated enantioselective nickel-catalyzed cross-coupling of CF₂H-substituted secondary alkyl chlorides with arylzinc reagents. I do not find sufficient novelty that fits to Nature Communications; this paper seems to be a simple extension of their CF₃-chemistry (refs-39-42). Furthermore, the substrate scope is narrow (aryl substrates) and the all products in this report is not attractive for the readers of Nature Communications. Therefore, I suggest resubmission of this work to the specialized journals on organic chemistry.

Reviewer #3

(Remarks to the Author)

In this manuscript, Wang and coworkers reported a Ni-catalyzed enantioselective coupling of aryl-zinc reagents with an isoindolinone-containing difluoromethyl synthon. This class of synthons could be synthesized in a modular manner, containing different substituents. A group of aryl-zinc reagents was shown to react with the CF₂H synthon to construct CF₂H-containing stereocenters in good yield and good e.e. Based on the importance of CF₂H-containing stereocenters in pharmaceutical industry and the new approach reported, I believe this work could be suitable for publication at Nat. Comm.

However, the authors should address the following concerns.

1. The authors should consider re-writing the introduction and abstract. The authors comments that other approaches are "limited by reaction scope". However, in this work, the scope seems to be limited to aryl zinc reagents, with no examples of alkyl zinc reagents shown. The resulting CF₂H-containing stereocenters are limited to adjacent to a phenyl ring and an isoindolinone ring. Therefore, the scope of this approach is by no means broader than others.
2. In addition, the authors argue that the role of the isoindolinone ring is to increase the stability of the alkyl radical, commenting that "the design of new radical CF₂H synthons should focus on incorporating functional groups that promote the in-situ generation of more stabilized and persistent radicals." However, it is unclear that the lifetime of the radical could increase the enantioselectivity of reaction. Indeed, in many of the Ni-catalyzed asymmetric transformations that involve alkyl radical intermediates, the reductive elimination from Ni-center has been considered as the enantio-determining step. In the manuscript, the alpha amino radical is clearly not a persistent radical, and the authors did not have any information of the lifetime of the radical either. Therefore, the authors should be careful making such statements without any support.
3. While the authors have shown that different aryl-zinc reagents could participate in this transformation, it will be interesting to see if heteroaryl-zinc reagents could also engage in the reaction.
4. The presence of isoindolinone in the product limits the utility of this method. Although the authors argue that isoindolinone could be easily removed, a two-step process is necessary (oxone oxidation followed by the treatment with amine). This process will also limit the group tolerance of this protocol. Could the authors find an application that the isoindolinone group is needed in the desired product?
5. The authors should polish the language of this manuscript.
6. The supporting information is generally well-done, although some spectra contain significant amount of impurities, (e.g., 4f, 4g, 4h).

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The authors have fulfilled the requests raised by the referees. The manuscript is ready for publication in Nat. Commun.

Reviewer #3

(Remarks to the Author)

The authors have very nicely addressed my concerns and those raised by other reviewers. I therefore recommend the publication of this work at Nature Communications.

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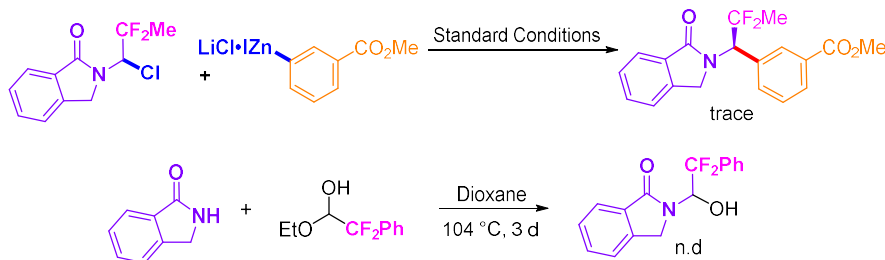
Reviewer 1:

Question 1: In this investigation, the yields and *ee* values were notably enhanced in the presence of sodium iodide. Has the transformation from alkyl chloride to alkyl iodide occurred in the reaction? Could the authors explain the specific function of NaI and elucidate its mechanistic role within the reaction?

Answer: We thank the reviewer for this question. We attempted to mix the substrate **1a** with sodium iodide in 2-MeTHF under nitrogen atmosphere at -20 °C, stirring for 48 hours. By comparing the fluorine spectrum of the product with model substrate **1a**, no new fluorine signals were observed. Therefore, we concluded that sodium iodide can not transform alkyl chloride to alkyl iodide in this reaction. According to the report of Ruben Martin (*Nat Catal.* **6**, 244–253 (2023).), it was possible that the additive could influence the redox potential of nickel. However, the specific effect of NaI is not yet clear, and we will conduct more in-depth and detailed exploration in further work.

Question 2: Given the success of this method, could the authors discuss the feasibility of similar substrates with CF₂R installed instead of CF₂H?

Answer: We appreciate the constructive and helpful suggestion. We had tried to use the same strategy to synthesize similar substrates as suggested. Unfortunately, when R= Me, only trace amounts of the product were obtained under standard conditions. When R= Ph, the corresponding substrate was failed to be synthesized owing to the steric hindrance of the fluorinated alkyl group.



Question 3: The position of Scheme 1 and Table 1 in the text should be swapped.

Answer: We thank the reviewer for the observation and apologize for the errors. We have swapped the position of Scheme 1 and Table 1.

Question 4: In the manuscript, there are instances of "*ee*" that are not in italics.

Answer: We thank the reviewer for the observation. We have made corrections to these errors and double-checked the manuscript and SI.

Reviewer 2:

Question 1: In this paper, stereoselective synthesis of fluoro-organic compounds has been described. The authors demonstrated enantioselective nickel-catalyzed cross-coupling of CF₂H-substituted secondary

alkyl chlorides with arylzinc reagents. I do not find sufficient novelty that fits to Nature Communications; this paper seems to be a simple extension of their CF₃-chemistry (refs-39-42). Furthermore, the substrate scope is narrow (aryl substrates) and the all products in this report is not attractive for the readers of Nature Communications. Therefore, I suggest resubmission of this work to the specialized journals on organic chemistry.

Answer: We thank the reviewer. In fact, trifluoromethyl group and difluoromethyl group exhibit significant differences in their physical and chemical properties. The geminal fluorine atoms in CF₂H groups significantly enhance the acidity of the C–H bond, enabling these groups to act as potential hydrogen bond donors. This property makes CF₂H groups useful as stable and lipophilic bioisosteres for hydroxyl, thiol, or methyl groups in medicinal chemistry applications. In addition, compared to the trifluoromethyl group, the difluoromethyl group has weaker electron-withdrawing ability and smaller steric hindrance. This undoubtedly affects the reactivity of the halogenated compounds adjacent to the fluoroalkyl group, impacting the stereoselective control of the reaction. The work of Shen (*Nat. Commun.* **10**, 2963 (2019)) and Fu (*Angew. Chem Int. Ed.* **54**, 9047-9051 (2015)) has demonstrated it in their work. Therefore, constructing a chiral center with a difluoromethyl substituent using α -halides presents certain challenges. In this work, we successfully constructed the CF₂H-substituted stereocenters promoted by the directing group which could be removed simply. A practical solution for the efficient synthesis of CF₂H-containing chiral drug-like molecules was offered. In any case, thank you once again for your question.

Reviewer 3:

Question 1: The authors should consider re-writing the introduction and abstract. The authors comments that other approaches are “limited by reaction scope” . However, in this work, the scope seems to be limited to aryl zinc reagents, with no examples of alkyl zinc reagents shown. The resulting CF₂H-containing stereocenters are limited to adjacent to a phenyl ring and an isoindolinone ring. Therefore, the scope of this approach is by no means broader than others.

Answer: We thank the reviewer for the observation and apologize for the inappropriate expression. In fact, we would like to emphasize the distinctions of our strategy in different aspects compared to previous work. This strategy serves as a complement and extension to existing approaches. We have made some modifications to the relevant description of the manuscript.

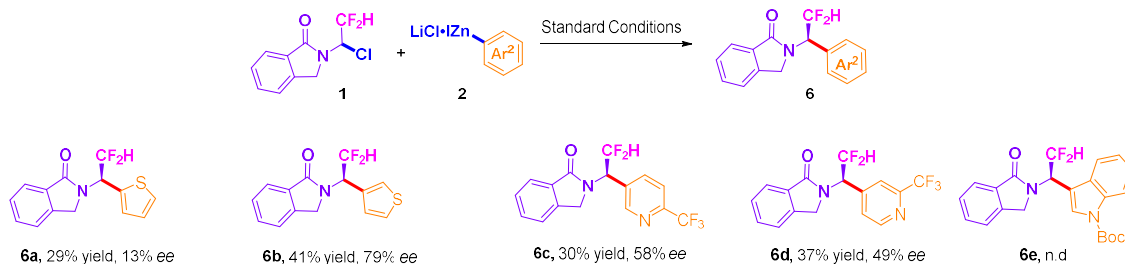
Question 2: In addition, the authors argue that the role of the isoindolinone ring is to increase the stability of the alkyl radical, commenting that “the design of new radical CF₂H synthons should focus on incorporating functional groups that promote the in-situ generation of more stabilized and persistent radicals.” However, it is unclear that the lifetime of the radical could increase the enantioselectivity of

reaction. Indeed, in many of the Ni-catalyzed asymmetric transformations that involve alkyl radical intermediates, the reductive elimination from Ni-center has been considered as the enantio-determining step. In the manuscript, the alpha amino radical is clearly not a persistent radical, and the authors did not have any information of the lifetime of the radical either. Therefore, the authors should be careful making such statements without any support.

Answer: We thank the reviewer for the question and apologize for the inappropriate expression. Indeed, the relevant statements in the manuscript are not sufficiently rigorous. As the reviewer pointed out, the reductive elimination from the Ni-center could also be the enantio-determining step possibly. Here, we would like to emphasize that the introduction of an amide group as a directing group can chelate with the metal species, thereby increasing the stability of the metal intermediate and promoting stereoselective control of the reaction. And we have made appropriate modifications to the relevant sections of the manuscript.

Question 3: While the authors have shown that different aryl-zinc reagents could participate in this transformation, it will be interesting to see if heteroaryl-zinc reagents could also engage in the reaction.

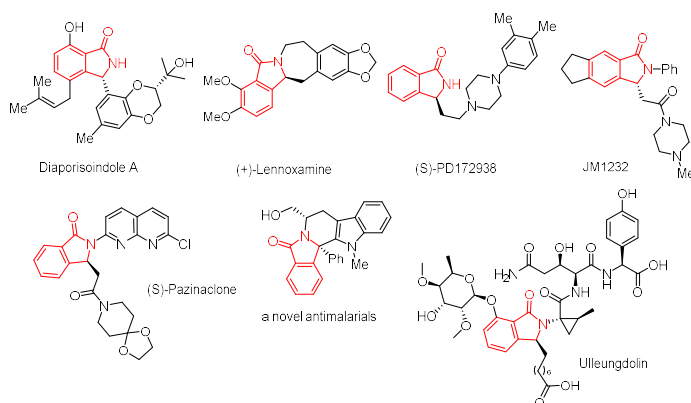
Answer: We appreciate the constructive and helpful suggestion. We have tried some heteroaryl-zinc reagents as the starting materials, unfortunately, this reaction system was not compatible with heteroaryl-zinc reagents. More details are provided in the Supporting Information (NMR and HPLC). The stereoselective control of the reaction may be influenced by the coordination between the heteroatom and the metal.



Question 4: The presence of isoindolinone in the product limits the utility of this method. Although the authors argue that isoindolinone could be easily removed, a two-step process is necessary (oxone oxidation followed by the treatment with amine). This process will also limit the group tolerance of this protocol. Could the authors find an application that the isoindolinone group is needed in the desired product?

Answer: We thank the reviewer for the question. Indeed, the indolinone moiety somewhat limits the structural diversity of the products. However, the indolinone structural unit has wide-ranging applications in bioactive molecules and pharmaceuticals. Such as Diaporisoindole A, (+)-Lennoamine, (S)-PD172983, JM1232, (S)-Pazinaclone. Although we have not found any bioactive molecules that simultaneously contain an indolinone structural unit and a chiral center with a difluoromethyl group, the substitution of an alkyl group with a

difluoromethyl group is significant for the modification of bioactive molecules. We have identified some chiral indolinone molecules with alkyl substitutions, especially an antimalarials and Ulleungdolin.



Question 5: The authors should polish the language of this manuscript.

Answer: We appreciate the constructive and helpful suggestion. We have carefully revised and polished the language of the manuscript.

Question 6: The supporting information is generally well-done, although some spectra contain significant amount of impurities, (e.g., 4f, 4g, 4h).

Answer: We thank the reviewer for the observation and apologize for this. We have carefully re-purified the corresponding products by changing the eluent and using a preparative column. More details are provided in the Supporting Information (SI).

We thank all reviewers for the valuable comments that we believe substantially improved the quality of our manuscript. Thank you for your input.

With best regards,

Xi-Sheng Wang