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Peer Review File

Defluorinative Functionalization Approach led by Difluoromethyl Anion Chemistry

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

This manuscript from Nagaki and co-workers describes the reductive generation of difluoromethyl anion from the corresponding trifluoromethyl precursor using K-napththalenide. This reaction, based on a 2 electrons reduction, requires the use of continuous flow to control the highly reactive intermediate. The use of flash chemistry is mandatory to master te high reactivity.
The optimized reaction conditions allowed the reduction of a large panel of CF3 derivatives and the reaction scope is fairly decent, with good to excellent yields. The functional group tolerance and the panel of compatible electrophiles is also good. This method is thus an interesting approach to convert the a priori poorly reactive CF3 residue into difluoromethylated compounds. The synthetic added value is crystal clear and this work is of high interest. I do believe that this work can be published in Nature Communications. However, before publication, some revisions are required.
1/ The batch flow comparison has to be introduced in the manuscript for the sake of the reader. Likewise, the IR analysis has to be added in the discussion.
2/ A detailed analysis of the redox potential of the K-napththalenide (as well the Na and Li analog), the CF3 model substrate has to be introduced in the manuscript. Indeed, the 2 electrons reduction should be justified with these data.
3/ Did the authors try fluoxetine?
4/ Could acid chloride, boron derivatives, imines be used as electrophiles? If these substrates are not reactive, a note should be added.
5/ A significant scale-up should be carried out.
6/ Supporting information: Some compounds are not characterized, they should be. In my opinion, GC yields or 19F NMR yields are not satisfactory, yet. TO demonstrate the synthetic utility, an isolated yield should be given.
The authors should mention if the 19F NMR is coupled decoupled from 1H. In addition, some multiplicities have to be confirmed, eg. 3d: the 2F are diastereotope and should be different. Moreover, IR and HRMS analyses are missing. In summary, a careful modification of the SI is needed before any publication.
In addition; pictures from the setup would be appreciated by the readership to figure out the simplicity and to popularize flash chemistry.
Hence, I cannot recommend this work for publication in Nature Communications in its current form, major revisions are required. Once, the above-mentioned points are addressed I would be pleased to recommend it for publication in Nature Communications.

Reviewer #2 (Remarks to the Author):

The authors report a transformation of CF3 group to other CF2-X units with variety of X through difluoromethyl anion species.
The reaction path via the anion seems to be quite difficult but a microflow system realized the process.
Substrate scope and application to synthesis of useful compounds are fascinating.

The reviewer has some questions.
Can more than C1 unit be applicable?
Is aryl group necessary for ET?

If ortho-propenyl group is attached on the starting CF3 material, is radical trapping observed against to the formation of anion. If it is not trapped, second SET would be very fast.

Nature Communication requiems high level of results and relating knowledge, and thus, the questions should be clarified.

After consideration of the questions, the reviewer thinks the manuscript would be publishable in Nat. Commun.

Response to referees
Reviewer Comment
Reviewer #1 :

This manuscript from Nagaki and co-workers describes the reductive generation of difluoromethyl anion from the corresponding trifluoromethyl precursor using K-napthalenide. This reaction, based on a 2 electrons reduction, requires the use of continuous flow to control the highly reactive intermediate. The use of flash chemistry is mandatory to master the high reactivity.

The optimized reaction conditions allowed the reduction of a large panel of CF_3 derivatives and the reaction scope is fairly decent, with good to excellent yields. The functional group tolerance and the panel of compatible electrophiles is also good. This method is thus an interesting approach to convert the a priori poorly reactive CF_3 residue into difluoromethylated compounds. The synthetic added value is crystal clear and this work is of high interest. I do believe that this work can be published in Nature Communications. However, before publication, some revisions are required.

→ We appreciate your reviewing.

1/ The batch flow comparison has to be introduced in the manuscript for the sake of the reader. Likewise, the IR analysis has to be added in the discussion.

→ We appreciate your suggestion and agree to introduce the data of the batch reaction in the manuscript. The IR data are presented in the Supplementary Materials rather than in the manuscript due to space limitations, but will be presented within the manuscript if necessary.

2/ A detailed analysis of the redox potential of the K-napthalenide (as well the Na and Li analog), the CF_3 model substrate has to be introduced in the manuscript. Indeed, the 2 electrons reduction should be justified with these data.

→ We appreciate your suggestion and agree that the reduction potential of the metal napthalenide is extremely significant for defluorinative functionalization of trifluoromethyl groups. However, it is difficult to calculate the reduction potential of napthalenide anion including counter cations. In fact, its reduction potential has been reported as the napthalenide anion ($C_{10}H_8^-$) without counter cations is E (THF)= –3.10 V (*Chem. Rev.* **1996**, *96*, 877–910.). Presumably, the reduction potential of napthalenide anion including counter cations would be reduced (E > –3.10 V). However, the reduction potential of trifluoromethyl arenes is approximately E= –2.50 V (*J. Am. Chem. Soc.* **2020**, *142*, 9181–9187.), and the reduction potential is low compared with the napthalenide anion. Hence, it is reasonable that the trifluoromethyl compound undergoes a two-electron reduction. To clarify, we added the following sentences to the manuscript.

"The reduction potential of napthalenide anion ($C_{10}H_8^-$) is E (THF)= –3.10 V (*Chem. Rev.* **1996**, *96*, 877–910.). Although the reduction potential of napthalenide anion including counter cations would be reduced (E > –3.10 V), the reduction potential of trifluoromethyl arenes is approximately E= –2.50 V (*J. Am. Chem. Soc.* **2020**, *142*, 9181–9187.). Thus, we speculated that the trifluoromethyl compound undergoes a two-electron reduction."

3/ Did the authors try fluoxetine?

→ We have tried fluoxetine for hydrodefluorination. Unfortunately, it gave the corresponding product only a trace under our standard conditions.

4/ Could acid chloride, boron derivatives, imines be used as electrophiles? If these substrates are not reactive, a note should be added.

→ We appreciate your suggestion. We have used benzoyl chloride as acid chloride to give the corresponding compound **3h**. In addition, we have tried imines as an electrophile, which obtained the target product in good yield. Although we attempted 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and triisopropyl borate as boron derivatives, were unsuitable as electrophiles for this reaction. The compounds with an electron-withdrawing group and a boryl group at the benzyl position are unstable (e.g. *Chem. Lett.* **2020**, *49*, 1439–1442.). Therefore, the corresponding product was probably decomposed. Thus, we added this entry (**Fig. 3, 3i**) and the following sentences in the manuscript.

"As well as imine was suitable for electrophile (**3i**)."

"On the other hand, boron derivatives (2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and triisopropyl borate) as electrophile were not appropriate for this reaction. The corresponding product with fluorine atoms and a boryl group at the benzyl position was probably unstable and decomposed."

5/ A significant scale-up should be carried out.

→ We appreciate your suggestion, and the flow reaction is easy to scale-up due to simply continuing to react. We have already reported continuous synthesis in the flow system. We demonstrated that carried out the synthesis of **3d** by continuous flow reaction for 23 min. To clarify this, we added the following sentences to the manuscript.

"Notably, gram-scale synthesis on the **3d** was also easily achieved by continuous operation for 23 min, obtaining the corresponding compound in 3.06 g."

6/ Supporting information: Some compounds are not characterized, they should be. In my opinion, GC yields or ^{19}F NMR yields are not satisfactory, yet. To demonstrate the synthetic utility, an isolated yield should be given.

→ We agree that GC yields or ^{19}F NMR yields are not completely satisfactory. To demonstrate the wide range of substrate adaptation in this study, we investigated various substrates. However, volatile products are difficult to isolate and inaccurate in an isolated yield. This is due to the properties of fluorine atoms and is a problem for many chemists. However, we consider that ^{19}F NMR yields are highly accurate. Actually, a lot of chemists adapt ^{19}F NMR yields for yield calculations for volatile products including fluorine atoms instead of isolated yields (eg. *Angew. Chem. Int. Ed.* **2018**, *57*, 1381–1385., *Org. Lett.* **2013**, *15*, 5134–5137., *Angew. Chem. Int. Ed.* **2011**, *50*, 3793–3798., *Nat. Commun.* **2018**, *9*, 1170–1179., *Angew. Chem. Int. Ed.* **2011**, *50*, 7655–7659.). Furthermore, we believe that the Late-stage functionalization demonstrates the synthetic utility of our reactions, and all isolable products are calculated in isolated yield.

7/ The authors should mention if the ^{19}F NMR is coupled decoupled from ^{1}H.

→ We appreciate your suggestion, and we have not carried out decoupled the ^{19}F NMR from ^{1}H.

8/ In addition, some multiplicities have to be confirmed, eg. **3d**: the 2F are diastereotope and should be different. Moreover, IR and HRMS analyses are missing. In summary, a careful modification of the SI is needed before any publication.

→ We appreciate your suggestion, and we recognize the 2F of **3d** are diastereotopic and non-

equilavent. However, these diastereotopes are observed as a single peak by NMR in the known compounds (e.g. **3d**) reported (*J. Am. Chem. Soc.* **2018**, *140*, 9404‑9408.). But to clarify it, we added IR and HRMS analyses to compounds bearing diastereotope (see Supplementary Materials).

9/ In addition; pictures from the setup would be appreciated by the readership to figure out the simplicity and to popularize flash chemistry.

→ We agree that the picture of the flow setup is significant. Thus, to clarify it, we added the flow reactor (see Supplementary Materials).

Reviewer #2:

The authors report a transformation of CF_3 group to other CF_2-X units with variety of X through difluoromethyl anion species.

The reaction path via the anion seems to be quite difficult but a microflow system realized the process. Substrate scope and application to synthesis of useful compounds are fascinating.

→ We appreciate your reviewing.

The reviewer has some questions.

1/ Can more than C1 unit be applicable?

→ We appreciate your question and are now interested in more than a C1 unit. Probably, perfluoroalkyl group also can be applied to C(sp^3)‑F defluorinative functionalization at benzylic position. Recently, Yasuda, Nishimoto et al. reported allylation of perfluoroalkylarenes at the benzylic position by a single-electron transfer from a photoredox catalyst (reference 18). Thus, there is also a possibility that anion species can be generated and reacted at the benzyl position of perfluoroalkylarenes under our condition, and this is currently under investigation and will be reported in due course.

2/ Is aryl group necessary for ET?

→ We appreciate your question and aryl group is not always necessary. Most important for ET is reduction potential of substrate. For example, defluorinative functionalization can be adapted to trifluoromethyl compounds bearing carbonyl groups without aryl group albeit in low yield. However, substrates bearing aryl groups are better. This may be due to the stability of the anion species.

3/ If ortho-propenyl group is attached on the starting CF_3 material, is radical trapping observed against to the formation of anion. If it is not trapped, second SET would be very fast.

→ We appreciate your suggestion and carried out a radical clock experiment using 2-Allyl(trifluoromethyl)benzene as substrate in our condition did not afford an intramolecularly cyclized product (see Supplementary Materials). Therefore, as you indicated, the second SET is considered very fast. To clarify this, we added the following sentences to the manuscript.

"Furthermore, we carried out a radical clock experiment to investigate the reaction rate of radical-polar crossover by the second single-electron transfer (Fig. 3c). Using 2-Allyl(trifluoromethyl)benzene as substrate in our condition did not afford an intramolecularly cyclized product (**4r'**), and hydrodefluorination product obtained (**4r**). Therefore, the second single-electron transfer is considered very fast."

REVIEWERS' COMMENTS

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I already reviewed this manuscript and after a careful examination of the revised version, I witnessed that the authors addressed most of the reviewers' comments.
Even though I am not convinced at all by the explanation regarding the isolated yields, as several compounds are not supposed to be volatile, I think this manuscript is now suitable for publication in Nature Communication.
Hence, I recommend this work for publication in Nature Communications in its current form. I do believe that this contribution is a nice piece of work that will be of high interest for the readership of the journal and the community.

Reviewer #2 (Remarks to the Author):

I have reviewed the revised manuscript submitted by Nagaki et al., which was initially evaluated based on my previous comments. The authors have made substantial revisions addressing the issues raised, and I am now satisfied with the improvements.

In light of the revisions, I believe the manuscript meets the standards for publication in Nature Communications.
I recommend that the manuscript be accepted for publication.

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→ We appreciate your reviewing and your recommendation for publication.

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→ We appreciate your reviewing and your recommendation for publication.