nature portfolio

Peer Review File

Dialkylation of CF2 unit enabled by cobalt electron-shuttle catalysis

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REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Huang and co-workers presented a cobalt-catalyzed multicomponent protocol for coupling of alkenes with bromodifluoromethyl sulfone, enabling dialkylation of CF2 unit to synthesize functionalized fluorinated compounds modularly from simple starting materials. A variety of electrophiles can be incorporated into the molecules, providing a new approach for access such building blocks that are otherwise difficult to generate. The reaction can be performed on multi-gram scale, demonstrating the practicality of this method. We think that this manuscript is suitable for publication on Nature Communications unless the following issues are addressed.

1. The aryl groups of the sulfone seem to be quite limited. Is there specific reason for this? The authors should clarify.

2. We suggested that it is more useful if the authors come up with a creative way to transform the aryl groups from the sulfone to other functionalities.

3. Did aryl-substituted alkenes work in this reaction? If not, what is the reason?

4. For the radical trapping experiments, is it possible to characterize by EPR? For the radical clock experiments, is it possible to observe the ring-opening process by incorporating a cyclopropyl into the alkene, which can undergo ring opening more rapidly?

Reviewer #2 (Remarks to the Author):

Huang and coworkers described a cobalt-catalyzed, modular synthetic approach for difluoromethylene compounds, involving the assembly of two C(sp3) fragments across a

CF2 unit in a single step. This method utilizes two π-unsaturated radical acceptors as starting materials and bromodifluoromethyl sulfone as the CF2 diradical synthon. The construction of a difluoromethylene group (CF2) presents challenges when employing traditional deoxofluorination and direct difluoromethylation methods. The authors have effectively managed this reaction through the radical addition of difluoromethyl radicals to two different π-unsaturated molecules. This method demonstrates compatibility with a wide range of coupling partners, including diverse olefins, iminiums, and hydrazones, showcasing its potential applications in synthetic organic chemistry. The paper is poised for publication after the resolution of following issues.

1. The sulfone moiety appears to play a crucial role in enhancing the stability and reactivity of the "CF2" diradical equivalents. Consequently, it is recommended to include relevant references focusing on fluorine manipulation with sulfone (sulfur). References such as (1) Chem. Rev. 2015, 115, 765-825; (2) Chem. Commun. 2021, 57, 8750-8753; (3) Angew. Chem. Int. Ed. 2016, 55, 2743-2747; and (4) Adv. Syn. Catal. 2019, 361, 5528–5533 would be beneficial.

2. The substrate scope screening section lacks discussion on aromatic amine-substituted N,O-acetals and conjugative alkenes. It would be valuable for the authors to provide examples and explanations if these substrates are utilized.

3. The authors state that zinc functions to reduce Co(II) to Co(I). However, it is plausible that zinc reacts with ArSO2CF2Br to form ArSO2CF2ZnBr. Therefore, conducting an experiment to exclude this pathway is recommended. Additionally, the authors should elaborate on the role of Mg(OTf)2 in the mechanism discussion.

4. The Supplementary Information lacks most of the product 19F NMR data coupling and splitting information, which requires a reasonable explanation. For mixture of diastereomers, it is advisable to specify the atom numbers regarding chemical shifts.

Reviewer #3 (Remarks to the Author):

The authors describe a multicomponent coupling reaction to synthesize CF2-containing carbogenic skeletons under cobalt catalysis. They demonstrate high chemoselectivity in the reaction sequence via domino radical relay pathway. The scope includes a range of functionalized alkenes and bromodifluoromethyl-heteroaryl sulfones, as well as a broad range of N,O-acetals or electron-deficient olefins. The method also can be applied to derivatize a number of natural compounds or bioactive compounds with good functional group compatibility. Lastly, the authors performed several control experiments, the findings suggest that the method involves Co-catalyzed single-electron transfer and Smiles rearrangement.

This is an interesting method, and the scope and synthetic applications of this work are broad and impressive. While engaging difuloroalkylative functionalization of alkenes in various cobalt and nickel coupling reactions is not new, using bromodifluoromethyl-heteroaryl sulfones in cobalt-catalyzed multicomponent reductive coupling reactions represent a new direction, and its acceptance in Nature Communications would be justified after some revisions considering the comments below.

1. Multicomponent coupling reaction often suffers from a lack of complete selectivity in the transfer of organic groups (this is particularly the case for radical relay coupling reactions). The authors did not investigate the potential side reactions and products (yields are often below 70%).

2. The outlined synthetic method has a limitation, it is suitable for the synthesis of heteroaryl substituted carbogenic skeletons, since the presence of an N-containing heteroaryl group is necessary for the preparation of the corresponding bromodifluoromethyl-heteroaryl sulfones. Therefore, this method does not provide access to simple aryl-substituted compounds. Hence, this information is not provided in the text or in Schemes. Accordingly, Ar is not a general substituent, but it is always a heteroaryl derivative. So, the authors have not developed a procedure for a wide range of Smiles rearrangements, but only for hereoaryl derivatives, which is still a significant improvement. A correct description of that inherent limitation is necessary.

3. Several related research works in difluoroalkylative functionalization of alkenes via cobalt-catalyzed three-component couplings reactions have been reported (Nat. Commun, 2021, 12, 4366; Chem. Sci. 2023, 14, 8672), which should be appropriately mentioned in the manuscript.

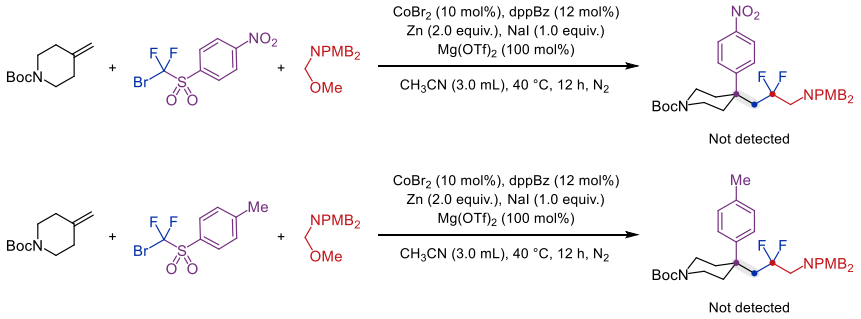
Reply to Reviewer #1's comments:

We sincerely appreciate the reviewer's thorough review and valuable suggestions, which have significantly contributed to clarifying the mechanism and enhancing the practicability of our work. We have addressed all the comments and made the necessary revisions to improve our manuscript.

Huang and co-workers presented a cobalt-catalyzed multicomponent protocol for coupling of alkenes with bromodifluoromethyl sulfone, enabling dialkylation of CF2 unit to synthesize functionalized fluorinated compounds modularly from simple starting materials. A variety of electrophiles can be incorporated into the molecules, providing a new approach for access such building blocks that are otherwise difficult to generate. The reaction can be performed on multi-gram scale, demonstrating the practicality of this method. We think that this manuscript is suitable for publication on Nature Communications unless the following issues are addressed.

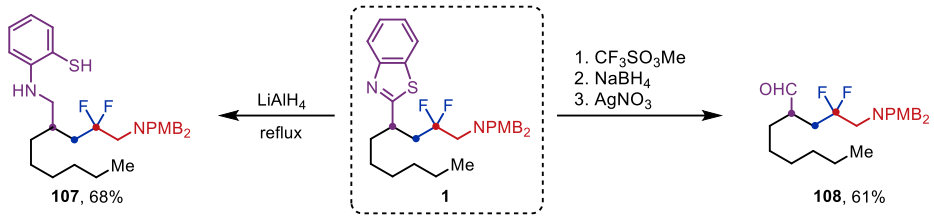
1. The aryl groups of the sulfone seem to be quite limited. Is there specific reason for this? The authors should clarify.

Reply: Thank you for pointing out this limitation. The migratory groups were generally limited to heteroaryl groups, typically thiazole and pyridine. We have attempted the reaction with (*p*-NO_2)$PhSO_2CF_2Br$ and (*p*-Me)$PhSO_2CF_2Br$, but failed to detect any corresponding products in the reaction mixture. These heteroaryl groups often feature lower aromaticity, making them more prone to undergo radical addition and subsequent Smiles rearrangement. For other aryl groups that exhibit a lower rate of Smiles rearrangement, competing side reactions, such as the radical addition to iminium ions, tend to occur, thereby hindering the generation of the desired product. We have revised the main text as "*However, simple aryl group-substituted sulfones were not suitable for this reaction, possibly due to their sluggish reactivity for intramolecular radical addition, which resulted in a diminished rate of Smiles rearrangement.*" to clarify and rationalize this limitation.



2. We suggested that it is more useful if the authors come up with a creative way to transform the aryl groups from the sulfone to other functionalities.

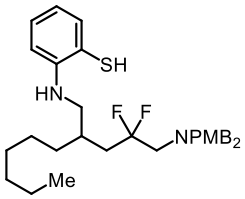
Reply: Thank you for your valuable suggestions. We have conducted the following synthetic transformations to showcase the transformation feasibility of the benzothiazole group. Through reductive ring-opening, the benzolthiazoyl in difluoroalkyl amine **1** could be smoothly converted into 2-aminobenzenethiol moiety (**107**), which is a key pharmacophore in drug discovery. Moreover, an operationally simple three-step one-pot treatment of **1** enabled the preparation of corresponding aldehyde **108** in good yield. These synthetic transformations have been incorporated into the main text as Fig. 6a.



Synthetic procedure for 107:

To a flame-dried Young type tube was added compound **1** (113 mg, 0.20 mmol, 1.0 equiv.), THF (1 mL), and 0.6 mL $LiAlH_4$ (1 M solution in THF) under N_2 atmosphere. The resulting mixture was stirred at reflux temperature for 12 hours, and then quenched by saturated aq. NH_4Cl (5.0 mL). The resulting mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product **107** as a yellow oil (78 mg, 68% yield).

2-((2-(3-(Bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)octyl)amino)benzenethiol (107).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 5H), 7.07 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.84 – 6.78 (m, 4H), 6.58 (d, *J* = 8.5 Hz, 1H), 6.45 (td, *J* = 7.4, 1.2 Hz, 1H), 4.99 (t, *J* = 5.9 Hz, 1H), 3.76 (s, 6H), 3.59 (s, 4H), 3.13 – 3.05 (m, 1H), 3.00 – 2.92 (m, 1H), 2.76 (t, *J* = 13.4 Hz, 2H), 1.94 – 1.84 (m, 1H), 1.84 – 1.70 (m, 2H), 1.43 – 1.34 (m, 1H), 1.33 – 1.16 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 149.6, 137.3, 132.1, 131.0, 130.4, 126.1 (t, *J* = 242.8 Hz), 118.2, 116.0, 113.8, 110.3, 58.4, 57.0 (t, *J* = 28.6 Hz), 55.3, 47.4, 36.7 (t, *J* = 22.8 Hz), 32.9, 32.0, 29.7, 26.4, 22.8, 14.3;

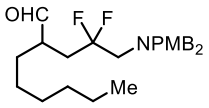
^{19}F NMR (471 MHz, $CDCl_3$) δ -96.8 (d, *J* = 245.0 Hz, 1F), -97.9 (d, *J* = 247.8 Hz, 1F);

HRMS (ESI) calcd. for $C_{33}H_{45}F_2N_2O_2S$ $[M+H]^+$: 571.3164, found: 571.3149.

Synthetic procedure for 108:

Compound **1** (567 mg, 1.0 mmol), activated 4Å powdered molecular sieves (1 g), and anhydrous CH_3CN (10 mL) was stirred at r.t. for 10 min, and then CF_3SO_3Me (197 mg, 1.2 mmol, 1.2 equiv.) was added. The suspension was stirred at r.t. for 2 hours and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of this crude *N*-methylbenzothiazolium salt in CH_3OH (10 mL) was added $NaBH_4$ (76 mg, 2.0 mmol, 2.0 equiv.). The mixture was stirred at r.t. for 30 min and then concentrated. The residue was diluted with acetone and filtered through a pad of Celite to remove excess $NaBH_4$, and then concentrated. To a vigorously stirred solution of this crude benzothiazolines in CH_2Cl_2 (3 mL) and CH_3CN (15 mL) were added H_2O (2 mL) and then $AgNO_3$ (340 mg, 2.0 mmol, 2.0 equiv.). The mixture was stirred at 45 °C for 2 hours, and then diluted with 1 M phosphate buffer at pH 7 (1 mL). Stirring was continued for an additional 15 min, and then the reaction mixture was diluted with 1 M phosphate buffer at pH 7 (10 mL) and partially concentrated to remove CH_3CN. The suspension was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a pad of Celite, and concentrated. The residue was purified by silica gel column chromatography to afford the desired product **108** as a colorless oil (281 mg, 61% yield for 3 steps).

2-(3-(bis(4-methoxybenzyl)amino)-2,2-difluoropropyl)octanal (108).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (dt, *J* = 2.6, 1.5 Hz, 1H), 7.25 – 7.17 (m, 4H), 6.90 – 6.82 (m, 4H), 3.80 (s, 6H), 3.65 – 3.52 (m, 4H), 2.77 (dd, *J* = 14.1, 12.4 Hz, 2H), 2.45 – 2.35 (m, 1H), 2.34 – 2.17 (m, 1H), 1.89 – 1.71 (m, 1H), 1.60 – 1.51 (m, 1H), 1.44 – 1.37 (m, 1H), 1.30 – 1.15 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H);

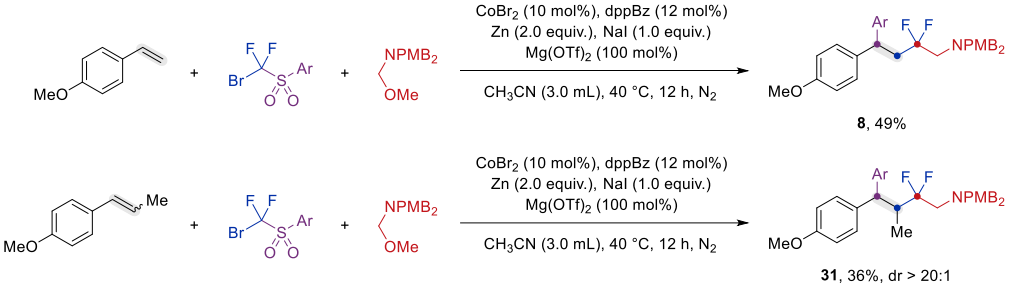
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 159.0, 130.9, 130.5, 125.2 (t, *J* = 242.5 Hz), 113.8, 58.5, 56.3 (t, *J* = 28.2 Hz), 55.4, 45.6, 33.8 (t, *J* = 23.9 Hz), 31.7, 29.7, 29.4, 26.6, 22.7, 14.2;

^{19}F NMR (376 MHz, $CDCl_3$) δ -96.1 (d, *J* = 249.9 Hz, 1F), -97.2 (d, *J* = 249.6 Hz, 1F).

HRMS (ESI) calcd. for $C_{27}H_{38}F_2NO_3$ $[M+H]^+$: 462.2814, found: 462.2807.

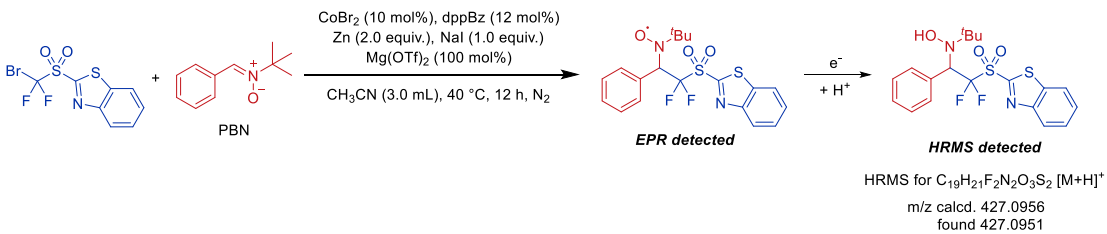
3. Did aryl-substituted alkenes work in this reaction? If not, what is the reason?

Reply: The aryl-substituted alkenes are compatible with this reaction, albeit with slightly attenuated reactivity. We previously provided one example with 4-methoxyl propenyl benzene (**29**) in Fig. 2a. To further demonstrate the applicability of such kind of substrates, we have added the reaction of 4-methoxystyrene as an additional example, which delivered the difluoroalkylated product **8** in 49% yield. The diminished reactivity may be attributed to the conjugative effect of the adjacent aryl group to the radical center, which hinders the Smiles rearrangement of the alkyl radical species.



4. For the radical trapping experiments, is it possible to characterize by EPR? For the radical clock experiments, is it possible to observe the ring-opening process by incorporating a cyclopropyl into the alkene, which can undergo ring opening more rapidly?

Reply: We appreciate these constructive suggestions. To further confirm the existence of radical species in the reaction process, we conducted several EPR experiments:



HRMS for $C_{19}H_{21}F_2N_2O_3S_2$ $[M+H]^+$

m/z calcd. 427.0956
found 427.0951

First, a radical capture experiment of ((bromodifluoromethyl)sulfonyl)benzothiazole **S2** with PBN was conducted under standard conditions. The supernatant of the reaction mixture was taken out by capillary for EPR analysis, which shows a nonet signal. The general triplet character indicates the formation of PBN-bound radical species, which could be further ascribed to the spin adduct of

the $ArSO_2CF_2$ radical. The general triplet character of the signals is due to hyperfine splitting (hfs) of the unpaired electron to the isotope ^{14}N (I = 1, 99.64% natural abundance) and the signal shows additional hfs to one ^{1}H and one ^{19}F (I = 1/2, 100% natural abundance), giving a nonet with the simulated coupling constant A_N = 14.5 G, $A_{\beta\text{-}H}$ = 2.33 G, $A_{\gamma\text{-}F}$ = 1.36 G (1F). Only one fluorine atom splits the signal due to the inequivalent environment of the two fluorine atoms in the stereochemical structure, as we discussed in our previous work (*Nat. Catal.* **2023**, *6*, 847–857). The presence of this spin adduct was further confirmed by HRMS based on the detection of hydroxylamine, which was generated by the reduction of the spin adduct under reductive conditions. The results in EPR and HRMS demonstrated that the difluoroalkyl radical is generated in the catalytic system.

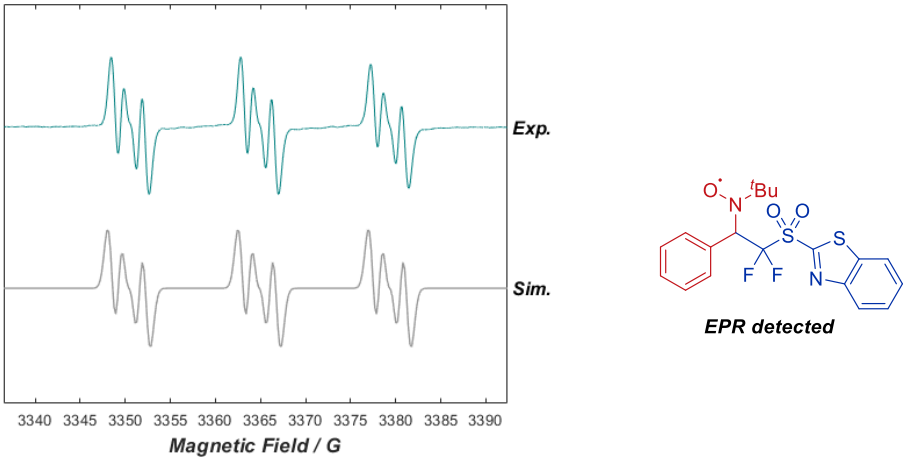
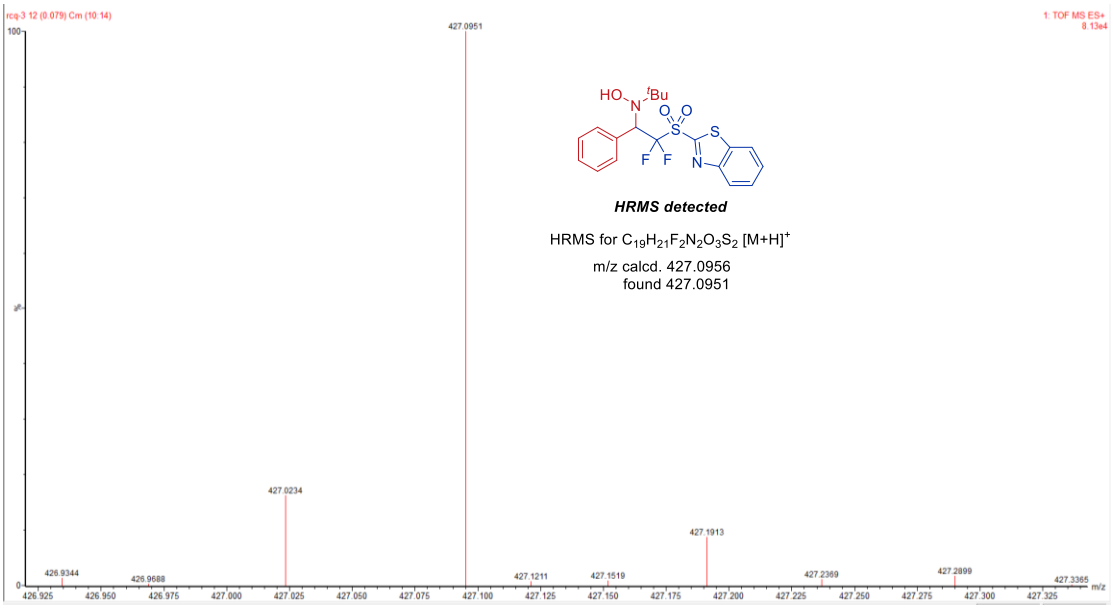
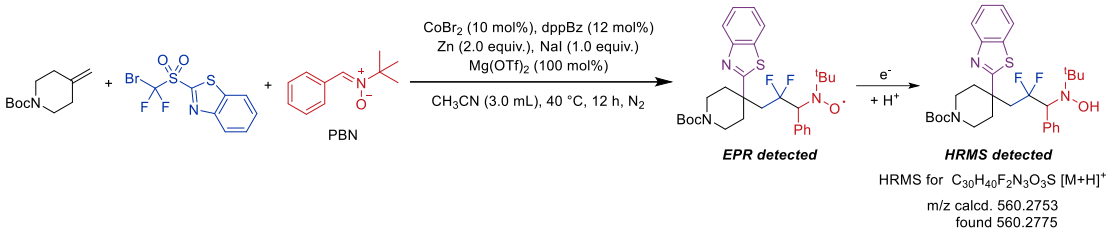


Fig. 1. Experimental (cyan line) and simulated (gray line) EPR spectra of spin adduct generated from $BrCF_2SO_2Ar$ under standard conditions with PBN as spin trap (A_N = 14.5 G, $A_{\beta\text{-}H}$ = 2.33 G, $A_{\gamma\text{-}F}$ = 1.36 G (1F)).





Meanwhile, we conducted the three-component radical capture experiment with *N*-Boc-4-methylenepiperidine, and a different nonet signal was detected by EPR, which was ascribed to the spin adduct of the three-component coupling product. The nonet signal shows hfs to one ^{14}N, one ^{1}H and two ^{19}F with the simulated coupling constant A_N = 14.4 G, $A_{\beta\text{-H}}$ = 2.35 G, $A_{\gamma\text{-F}}$ = 1.35 G (1F), 0.80 G (1F). Similarly, the three-component spin adduct was also detected by HRMS in the reduced form, demonstrating that the radical olefin addition and radical Smiles rearrangement process exist in the reaction.

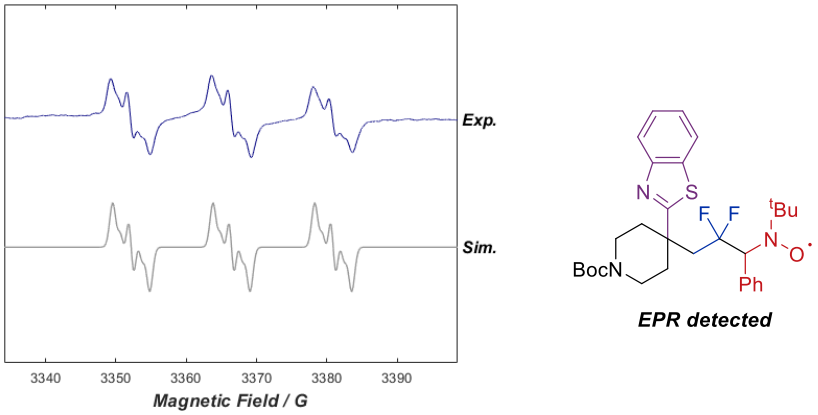
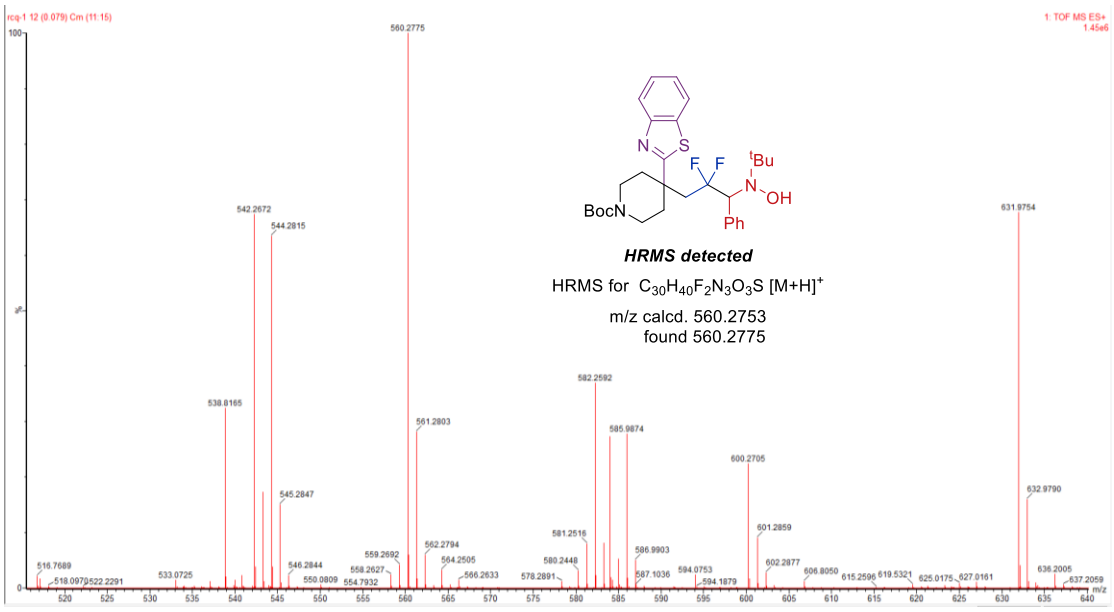
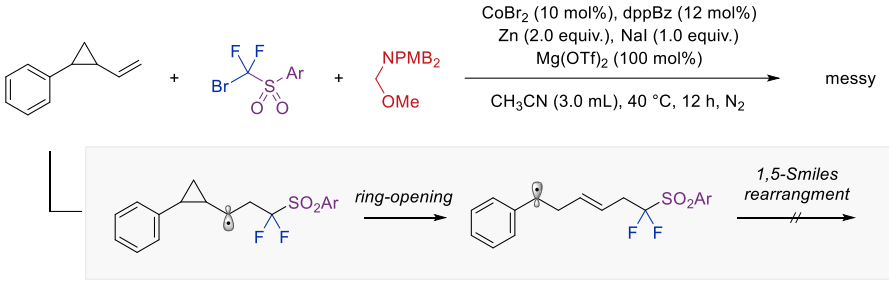


Fig. 2. Experimental (blue line) and simulated (gray line) EPR spectra of spin adduct generated from the three-component reaction under standard conditions with PBN as spin trap (A_N = 14.4 G, $A_{\beta\text{-H}}$ = 2.35 G, $A_{\gamma\text{-F}}$ = 1.35 G (1F), 0.80 G (1F)).



On the other hand, we attempted a radical ring-opening experiment with (2-vinylcyclopropyl)benzene as substrate under standard conditions, but failed to isolate desired product from the messy reaction mixture. Although the ring opening might have occurred, however,

the resulting radical species could not undergo 1,5-Smiles rearrangement smoothly to deliver the corresponding product due to the inappropriate radical position.



The above mechanism experiments have been incorporated into the manuscript as Fig. 5a to reinforce our discussion on the reaction mechanism.

Reply to Reviewer #2's comments:

We thank Reviewer 2 for his/her positive comments, detailed feedback and thoughtful suggestions to improve our manuscript, to which we have responded as follows.

Huang and coworkers described a cobalt-catalyzed, modular synthetic approach for difluoromethylene compounds, involving the assembly of two C(sp3) fragments across a CF2 unit in a single step. This method utilizes two π-unsaturated radical acceptors as starting materials and bromodifluoromethyl sulfone as the CF2 diradical synthon. The construction of a difluoromethylene group (CF2) presents challenges when employing traditional deoxofluorination and direct difluoromethylation methods. The authors have effectively managed this reaction through the radical addition of difluoromethyl radicals to two different π-unsaturated molecules. This method demonstrates compatibility with a wide range of coupling partners, including diverse olefins, iminiums, and hydrazones, showcasing its potential applications in synthetic organic chemistry. The paper is poised for publication after the resolution of following issues.

1. The sulfone moiety appears to play a crucial role in enhancing the stability and reactivity of the "CF2" diradical equivalents. Consequently, it is recommended to include relevant references focusing on fluorine manipulation with sulfone (sulfur). References such as (1) Chem. Rev. 2015, 115, 765-825; (2) Chem. Commun. 2021, 57, 8750-8753; (3) Angew. Chem. Int. Ed. 2016, 55, 2743-2747; and (4) Adv. Syn. Catal. 2019, 361, 5528–5533 would be beneficial.

Reply: These relevant works have been included as ref. 40 – 43.

ref. 40: Ni, C., Hu, M. & Hu, J. Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis. *Chem. Rev.* **115**, 765–825 (2015).

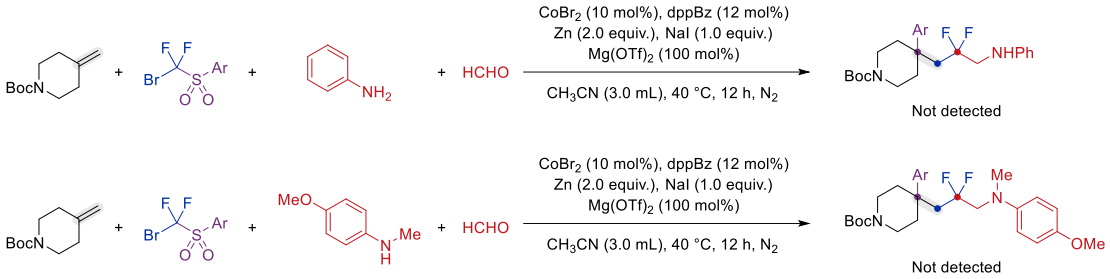
ref. 41: Rong, J. et al. Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **55**, 2743–2747 (2016).

ref. 42: Wei, J. et al. Transition-Metal-Free Electrophilic Fluoroalkanesulfinylation of Electron-Rich (Het)Arenes with Fluoroalkyl Heteroaryl Sulfones via C(Het)−S and S=O Bond Cleavage. *Adv. Synth. Catal.* **361**, 5528–5533 (2019).

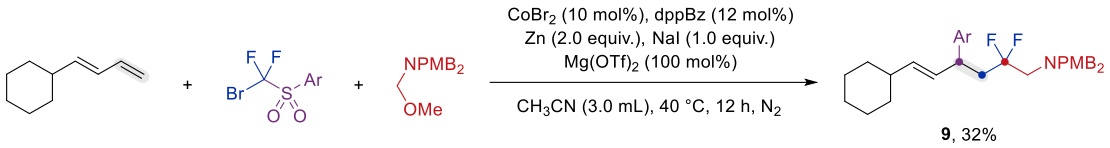
ref. 43: Zhou, X., Ni, C., Deng L. & Hu, J. Electrochemical reduction of fluoroalkyl sulfones for radical fluoroalkylation of alkenes. *Chem. Commun.* **57**, 8750–8753 (2021).

2. The substrate scope screening section lacks discussion on aromatic amine-substituted N,O-acetals and conjugative alkenes. It would be valuable for the authors to provide examples and explanations if these substrates are utilized.

Reply: Thanks for your advice. Due to the poor nucleophilicity of aromatic amines, synthesizing aromatic amine-substituted *N*,*O*-acetals from amines and paraformaldehyde is extremely challenging. We have attempted a four-component reaction with the in-situ condensation of aniline/4-methoxy-*N*-methylaniline and paraformaldehyde, but were unable to detect any desired product.



On the other hand, conjugative alkenes are amenable in this transformation. We have added an example with 4-cyclohexyl-1,3-butadiene (**9**) in Fig. 2a to demonstrate its applicability.



We have incorporated the example and corresponding discussion into the main text.

3. The authors state that zinc functions to reduce Co(II) to Co(I). However, it is plausible that zinc reacts with ArSO2CF2Br to form ArSO2CF2ZnBr. Therefore, conducting an experiment to exclude this pathway is recommended.

Reply: Thanks for your insightful comments. We have conducted additional mechanistic experiments to exclude the participation of organozinc reagent. Followed a procedure described by Hu and coworkers (*J. Fluorine Chem.*, **2017**, *198*, 67), we successfully synthesized the (2-pyridinylsulfonyl)difluoromethylzinc reagent (2-pySO_2CF_2ZnBr) by stirring the 2-pySO_2CF_2Br with zinc powder in DMF (the same procedure was failed to synthesize benzothiazolyl-derived zinc reagent). This organozinc reagent was tentatively assigned via its characteristic ^{19}F NMR spectrum, showing a singlet at -104.0 ppm, closed to the -105.6 ppm chemical shift of phenyl analogue reported by Hu. The hydrolysis byproduct, which exhibited a doublet at -125.8 ppm, was inevitably formed during the operation and NMR measurement. This organozinc reagent was subsequently subjected to the standard reaction in place of $ArSO_2CF_2Br$ and zinc powder, and this reaction resulted in a messy mixture in which no three-component coupling product **38** was detected. This result indicates that the organozinc reagent most likely did not participate in the reaction and is not efficient in delivering the product within the Co electron-shuttle catalytic system.

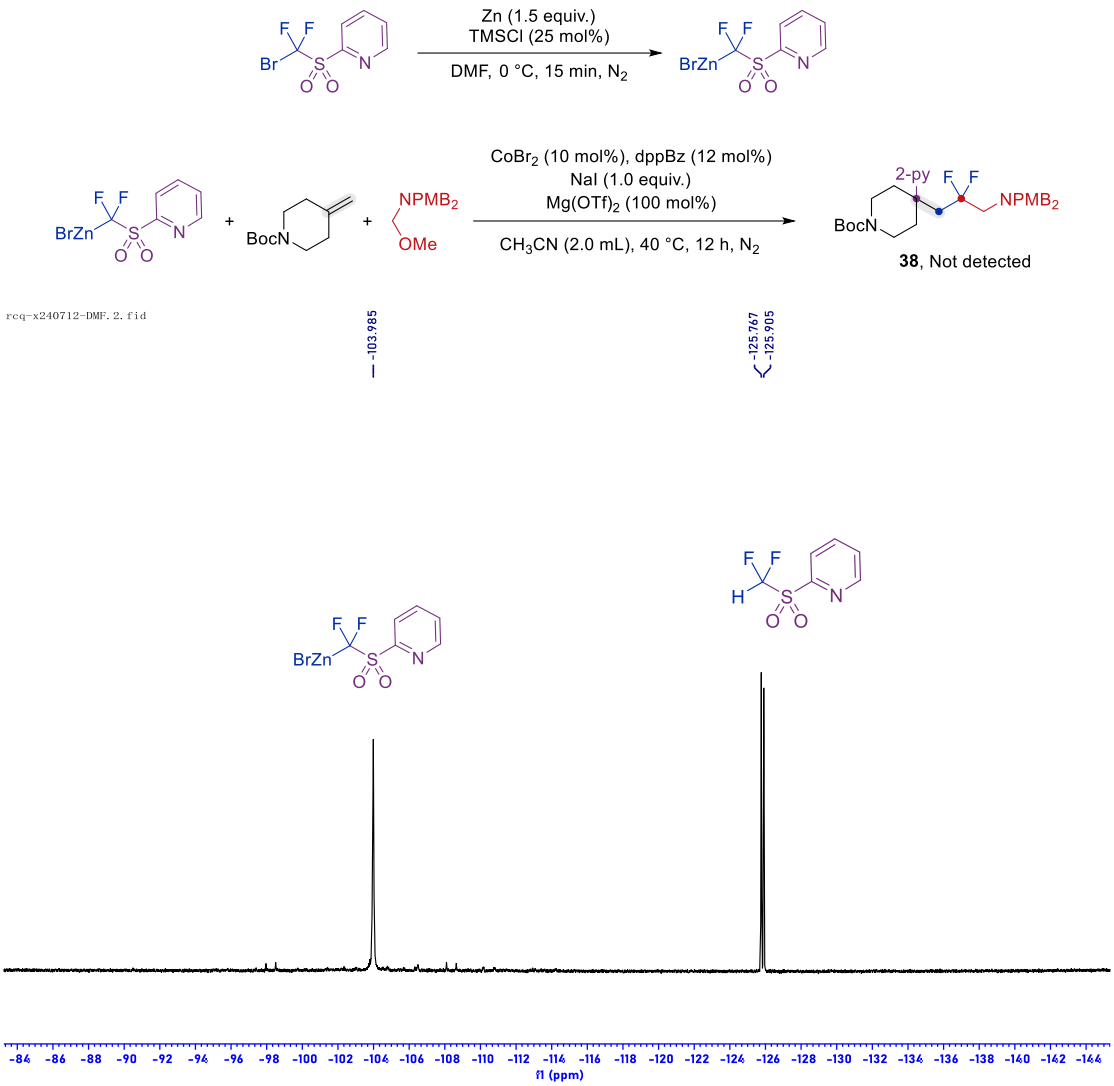


Fig. 3. The ^{19}F NMR spectra of (2-pyridinyl sulfonyl)difluoromethylzinc reagent prepared in DMF.

Reaction procedure:

In the glove box, zinc powder (59 mg, 0.90 mmol, 1.5 equiv.) was added into a Schlenk tube. Anhydrous DMF (1.5 mL) was added and the mixture was stirred at room temperature. Chlorotrimethylsilane (16 mg, 0.15 mmol, 25 mol%) was then added into the mixture to activate zinc powder. Five minutes later, 2-pySO_2CF_2Br (206 mg, 0.60 mmol, 1.0 equiv.) was added into the suspension. The reaction proceeded smoothly in 15 minutes to give (2-pyridinyl sulfonyl)difluoromethylzinc reagent. The mixture was kept at room temperature to precipitate the remaining zinc powder, and the solution was directly used for next step.

$CoBr_2$ (6.6 mg, 10 mol%), dppBz (16.1 mg, 12 mol%), and CH_3CN (3.0 mL) were added to a flame-dried Young-type tube under N_2 atmosphere. The resulting mixture was stirred at 40 °C for 30 minutes. After that, alkene (0.30 mmol, 1.0 equiv.), organozinc reagent (0.45 mmol, 1.5 equiv., 0.4 M in DMF), *N*,*O*-acetal (0.45 mmol, 1.5 equiv.), $Mg(OTf)_2$ (96.6 mg, 100 mol%), NaI (45 mg, 0.30 mmol, 1.0 equiv.) were added under N_2 atmosphere. The reaction mixture was degassed with freeze-thaw method for 3 times and stirred at 40 °C for 12 hours. After completion, the solvent was removed under reduced pressure and the residue was quenched by saturated aq. NH_4Cl (5.0 mL). The resulting mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na_2SO_4, filtered, and then analyzed by NMR spectra.

Additionally, the authors should elaborate on the role of Mg(OTf)2 in the mechanism discussion.

The $Mg(OTf)_2$ acts as a Lewis acid to activate the radical acceptors, thereby accelerating radical addition (for aminomethylation reactions, it promotes the formation of iminium ions). We have added the discussion on this role in the mechanistic study section.

4. The Supplementary Information lacks most of the product 19F NMR data coupling and splitting information, which requires a reasonable explanation. For mixture of diastereomers, it is advisable to specify the atom numbers regarding chemical shifts.

Reply: Thanks for your meticulous suggestions. The products – difluoroalkylated compounds – typically exhibit either a singlet signal (when the fluorine atoms are approximately magnetically equivalent) or two doublet signals (when the fluorine atoms are not magnetically equivalent) in ^{19}F NMR spectra. However, in some examples containing multiple stereoisomers (diastereomers or Z/E isomers), the ^{19}F NMR spectra can become complicated and difficult to interpret. We have carefully re-analyzed these spectra, assigned the peaks, and specified the atom numbers according to chemical shifts.

Reply to Reviewer #3's comments:

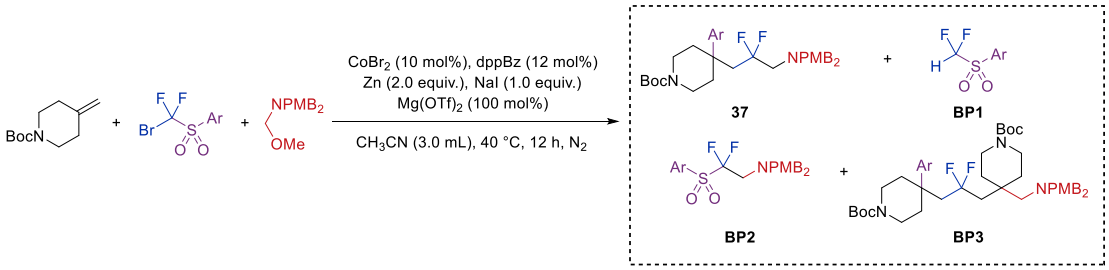
Reviewer 3 appropriately evaluates our results. We are grateful to Reviewer 3, who gave us valuable suggestions to support and improve our manuscript. We have revised the manuscript in response to the comments, which we believe have substantially strengthened our manuscript.

The authors describe a multicomponent coupling reaction to synthesize CF2-containing carbogenic skeletons under cobalt catalysis. They demonstrate high chemoselectivity in the reaction sequence via domino radical relay pathway. The scope includes a range of functionalized alkenes and bromodifluoromethyl-heteroaryl sulfones, as well as a broad range of N,O-acetals or electron-deficient olefins. The method also can be applied to derivatize a number of natural compounds or bioactive compounds with good functional group compatibility. Lastly, the authors performed several control experiments, the findings suggest that the method involves Co-catalyzed single-electron transfer and Smiles rearrangement.
This is an interesting method, and the scope and synthetic applications of this work are broad and impressive. While engaging difuloroalkylative functionalization of alkenes in various cobalt and nickel coupling reactions is not new, using bromodifluoromethyl-heteroaryl sulfones in cobalt-catalyzed multicomponent reductive coupling reactions represent a new direction, and its acceptance in Nature Communications would be justified after some revisions considering the comments below.

1. Multicomponent coupling reaction often suffers from a lack of complete selectivity in the transfer of organic groups (this is particularly the case for radical relay coupling reactions). The authors did not investigate the potential side reactions and products (yields are often below 70%).

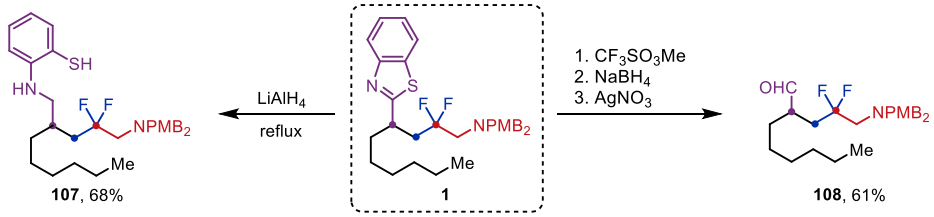
Reply: Thank you for pointing out this important detail. We agree that achieving selective control in multi-component radical coupling reactions is often challenging, and we have attempted to minimize the occurrence of side reactions by modifying the catalyst system and adjusting the

polarity match between radical species. In this reaction, the potential side products include (using the reaction to yield product **37** as an example) difluorosulfone (**BP1**), bi-component cross-coupling product of electrophiles (**BP2**), a little olefin double addition product (**BP3**), as well as trace amount of other unidentified byproducts. The loss of yield mainly stems from the remaining olefin material and the generation of byproduct **BP3**. These potential side reactions and products have been additionally mentioned in the Supplementary Information.



2. The outlined synthetic method has a limitation, it is suitable for the synthesis of heteroaryl substituted carbogenic skeletons, since the presence of an N-containing heteroaryl group is necessary for the preparation of the corresponding bromodifluoromethyl-heteroaryl sulfones. Therefore, this method does not provide access to simple aryl-substituted compounds. Hence, this information is not provided in the text or in Schemes. Accordingly, Ar is not a general substituent, but it is always a heteroaryl derivative. So, the authors have not developed a procedure for a wide range of Smiles rearrangements, but only for hereoaryl derivatives, which is still a significant improvement. A correct description of that inherent limitation is necessary.

Reply: We truly appreciate your detailed suggestions. We have revised the relevant discussion to more accurately describe this aryl scope. However, it is equally important to mention that benzothiazole is a transformative group that enables access to other functionalities such as aldehyde, as demonstrated in our additional synthetic transformations. Therefore, this method would offer ample opportunities for synthesizing various CF_2-containing functional molecules.



3. Several related research works in difluoroalkylative functionalization of alkenes via cobalt-catalyzed three-component couplings reactions have been reported (Nat. Commun, 2021, 12, 4366; Chem. Sci. 2023, 14, 8672), which should be appropriately mentioned in the manuscript.

Reply: These relevant works have been included as ref. 28, 29.

ref. 28: Cheng, X. et al. Organozinc pivalates for cobalt-catalyzed difluoroalkylarylation of alkenes. *Nat. Commun.* **12**, 4366 (2021).

ref. 29: Lin, J. et al. Salt-stabilized alkylzinc pivalates: versatile reagents for cobalt-catalyzed selective 1,2-dialkylation. *Chem. Sci.* **14**, 8672–8680 (2023).

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors have addressed this reviewer's concerns.

Reviewer #2 (Remarks to the Author):

[In confidential comments to the editorial office, this reviewer expressed that the manuscript is ready for publication.]