nature portfolio

Peer Review File

Copper-Catalyzed Highly Switchable Defluoroborylation and Hydrodefluorination of 1-(Trifluoromethyl)Alkynes

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

This manuscript submitted to Nat. Commun. describes a novel Cu-catalyzed highly switchable defluoroborylation and hydrodefluorination of trifluoromethylated alkynes, showcasing a remarkable ability to selectively generate four distinct CF2-containing compounds from a single substrate. The notable aspect of this transformation lies in its chem- and regio-selectivity, which can be readily controlled by adjusting the base and ligand quantities. The authors explicated the mechanism via control experiments and DFT calculations. This manuscript requires a major revision before its possible publication:
1.Various solvents are employed for condition A, B, and C. How can the solvent effect be elucidated? Could you provide some experimental and computational insights into the role played by these solvents?
2.The current form of the mechanistic DFT studies is somewhat crude and riddled with a few issues. And the presentation of the DFT outcomes is rather difficult to follow. To the point that it is distracting from the excellent synthetic work that is performed and reported. The DFT results need a major revision, and they ought to be organized in a manner that is more comprehensible and accessible.
3.The stereo configuration (Z/E) of compound 99 depicted in Fig 6 differs from that depicted in Fig 7-9. Assuming the correctness of the stereo configuration presented in Fig 6, it follows that all the mechanistic DFT studies conducted by the authors are erroneous. It is imperative for the authors to thoroughly reevaluate these studies.
4.There is also a major flaw in the interpretation of the computational results on the regio-selectivity of the Cu–B bond insertion into alkyne substrate 1 (Supplementary Fig5). This process is irreversible, due to its highly exothermic nature. The product stability difference doesn't control the rate of the irreversible reactions. Under the current mechanistic scenario, reverse regio-selectivity would be observed. Compound 100 should be obtained as the major intermediate.
Additionally, the current Supplementary Fig5 only provides numbers for the free energies of TSs and the intermediates, insights behind the numbers are lacking. It would be critical, if the authors can explain the origin of the difference between the TSs.
5.As to the calculated profiles, certain steps must be taken into account regarding the transitional state. For instance, in the Supplementary Fig4, the process of the O-H bond broken and the subsequent protonation necessitate a transition state that bridges A_Int1 and A_Int2, as well as a transition state that links A_Int2 to 99. The related calculations should be considered to check the rate-determining step. Moreover, the transition state for the transmetallation of LCu-OMe with B2(pin)2 also need to be calculated. Additionally, it is advisable to substitute Supplementary Figure 4 for Fig. 8 in the main text to mitigate any potential misunderstandings.
6.Given that this is an English language journal, the authors need to work with a native-English speaking copy editor to make the manuscript readable to the target audience.

Reviewer #2 (Remarks to the Author):

XXX reported Cu-catalyzed highly switchable defluoroborylation and hydrodefluorination of trifluoromethylated alkynes, which provides a rare instance of highly selective generation of four kinds of CF2-containing compounds from a single substrate. Synthetically, it is still very

novel to start from a single substrate and realize the obtaining of different products by simply changing the conditions of the reaction. However, it is worth pointing out that the present reaction is not very innovative in terms of the mechanism of the reaction in line with the aims of Nat. Commun journal, although the authors tried to illustrate the innovation of the reaction mechanism by means of DFT. Mechanistically, the core intermediate of this reaction is the regioselective addition of Cu-B to trifluoroalkynes in the first step, which leads to a number of subsequent transformations; the continued addition of Cu-B to trifluoromethyl olefins in the later step is a well-known process. And the protonolysis about alkenyl borate is likewise a known reaction. The authors' control experiments also show to some extent that it is possible to obtain the other three products from product 3 without copper catalysts. In addition, the reaction substrates in this paper are still very limited (diborylated scope is only 10). In addition, the reviewer speculates whether alkyl-substituted trifluoromethyl alkynes (e.g., 14 in Fig. 2) could also be used for the expansion of the next three types of products.

Reviewer #3 (Remarks to the Author):

Recommendation: Publish after major revisions are noted.
Comments:
The authors describe a Copper-Catalyzed Highly Switchable Defluoroborylation and Hydrodefluorination of 1-(Trifluoromethyl) Alkynes to access synthetically challenging CF2-containing compounds in simple and efficient ways. By simply altering the base, hydrodefluorination products of gem-difluoroalkenes or difluoromethylalkenes could also be selectively generated, making the work interesting and valuable to the synthetic community. Though Song and coworkers have already developed a Copper-Catalyzed diborylation of halotrifluoromethyl olefins (ref 36), via a similar strategy involving a beta-fluoride elimination by the copper intermediate. In light of this report, the present work is not entirely novel. A few points need to be addressed before it can be suitable for publication.
1. Will the reaction work for conditions B and C (Figures 3 and 4) with aliphatic alkynes? The author should show some examples with aliphatic substituents.
2. The requirement of 1 equiv. of Phen in condition B is not clear. The authors must study this carefully. It's hard to imagine why a weak Lewis basic additive would enable such reactivity.
3. In the case of Compound 14, What is the reason behind regioselectivity? According to DFT, regioselectivity comes from the aromatic substituent, which is absent in this case. Please comment.
4. The present method pertaining to Conditions C and D seems highly atom-uneconomical. I don't see any advantage in making these gem-difluoro compounds through this method. Justification on this front is not available in the main text.
5. In the case of Figure 3; after the monoborylation, the reaction mixture was filtered through a short plug of silica gel and washed with DCM as the eluent. Then, a coupling reaction was performed. This reaction is not an in-situ transformation but a two-pot sequential one.
6. Some of the compounds are impure. The 13C- peaks, in some cases, are too small (compounds 9, 13, 16, 19, 23, 40, 42, 50, 79, 92). In the case of few compounds, there are unidentified peaks in the 11B spectrum near 20 ppm. These must be addressed before publication.
7. In the case of Compound 91; the percentage of deuterium incorporation is missing.
8. 11B is missing for compounds 99 and 100.
9. Detailed analysis proof for the formation of compound 100 is missing.
10. There is no proof for the other isomerization of compound 101.
11. In the case of SI-42, the title page is added again. It must be removed before publication.

12. SI: [M+H]+ should be changed to [M+H]+ when writing the HRMS value.
13. SI: In the case of page S9, the footnote is missing for the table.

July 5, 2024

Thank all reviewers for your valuable feedback and time on our manuscript (ID: NCOMMS-24-01314-T). These comments are all valuable and helpful for improving our manuscript. According to these comments, we have made extensive modifications to our manuscript and supplemented extra data to make our results convincing. The reviewers' comments are laid out below in blue italicized font and specific concerns have been numbered. Our response is given in normal font and changes/additions to the revised manuscript are given in the yellow text.

Referee 1:

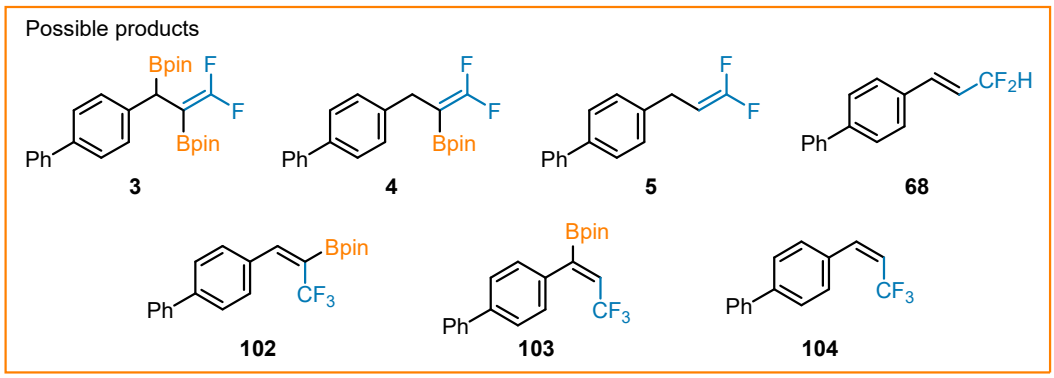
1. *"This manuscript submitted to Nat. Commun. describes a novel Cu-catalyzed highly switchable defluoroborylation and hydrodefluorination of trifluoromethylated alkynes, showcasing a remarkable ability to selectively generate four distinct CF2-containing compounds from a single substrate. The notable aspect of this transformation lies in its chem- and regio-selectivity, which can be readily controlled by adjusting the base and ligand quantities. The authors explicated the mechanism via control experiments and DFT calculations. This manuscript requires a major revision before its possible publication."*

   Response: We thank the reviewer for the positive comments on our manuscript.

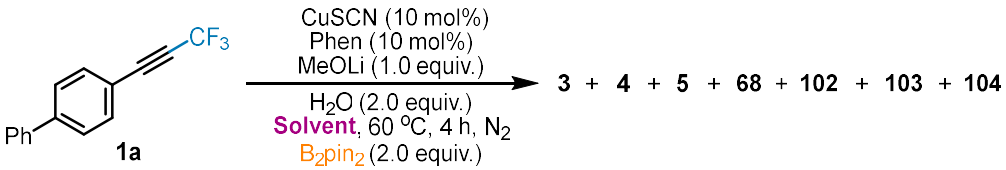
2. *"Various solvents are employed for condition A, B, and C. How can the solvent effect be elucidated? Could you provide some experimental and computational insights into the role played by these solvents?"*

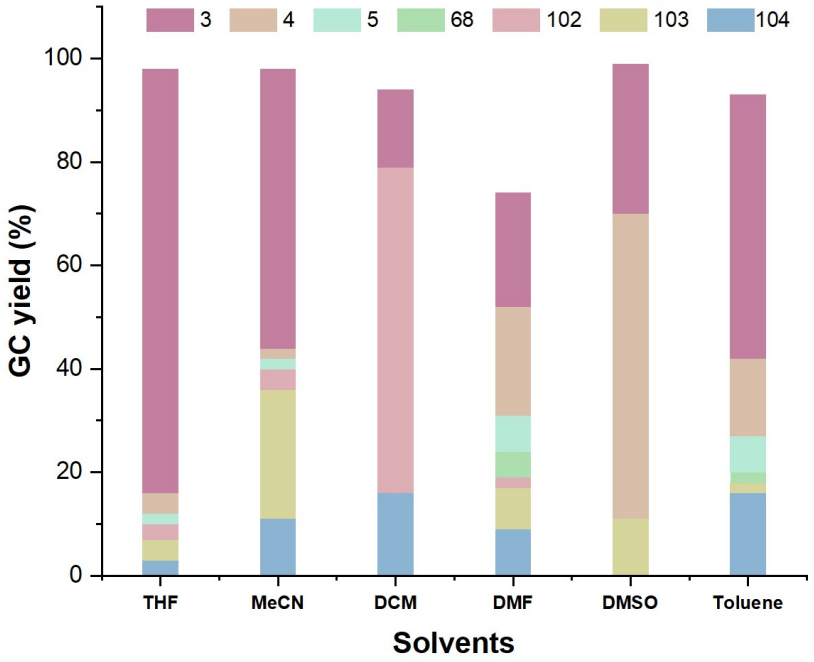
   Response: We greatly appreciate the reviewer's valuable comments. In line with the suggestion, we used **1a** as the feedstock and monitored the product distribution under conditions A, B, and C by varying the solvents. The results are presented in a stacked histogram below.

   As illustrated in the figure, the solvent type significantly affects the product distribution. Under condition A, product **3** was obtained in high yields in THF, MeCN, and toluene. However, in DMSO, further deborylation led to the formation of product **4**. Under condition B, product **4** was selectively produced in high yields exclusively in MeCN. In DMF, further deborylation resulted in product **5**, whereas in DMSO and toluene, both product **3** and product **4** were present in significant amounts. Under condition C, product **5** was the main product in THF, MeCN, and DCM, with the best reaction performance observed in DCM.



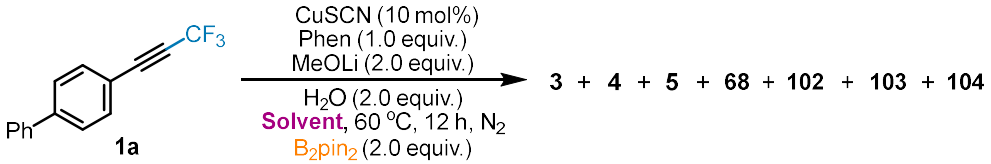
Condition A

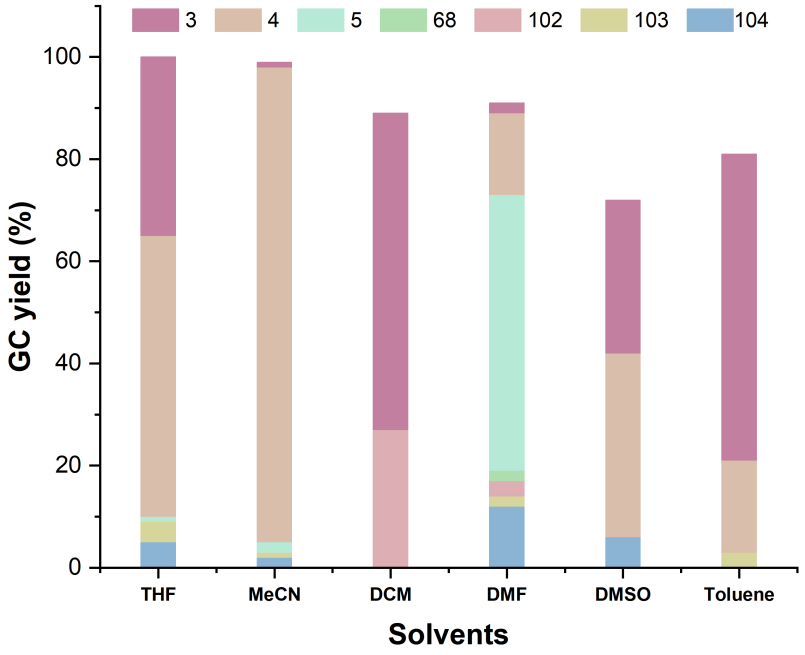




The yield was determined by GC using biphenyl as an internal standard.

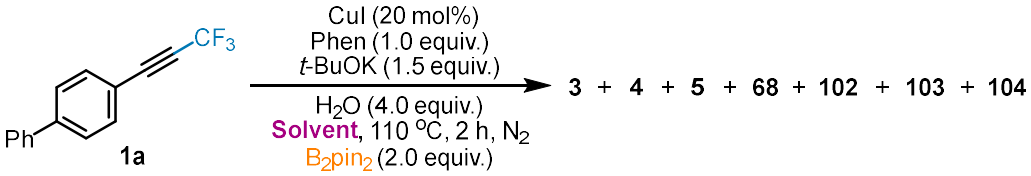
Condition B

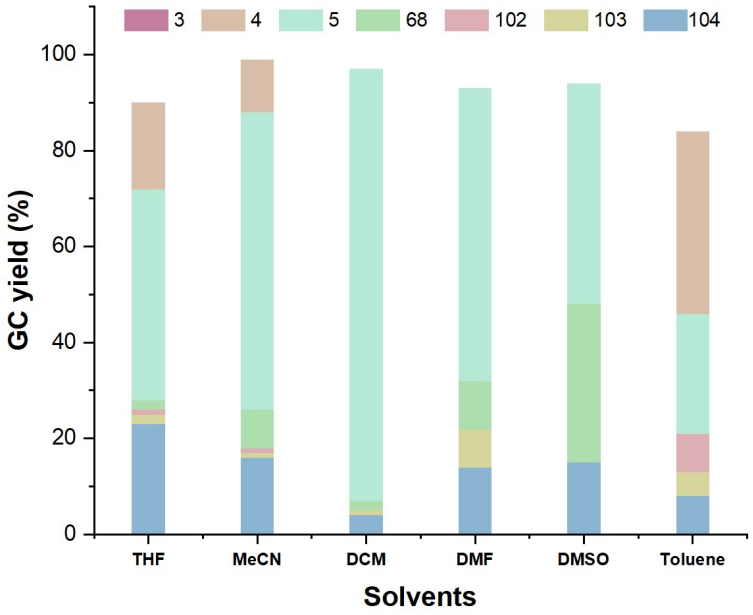




The yield was determined by GC using biphenyl as an internal standard.

Condition C





The yield was determined by GC using biphenyl as an internal standard.

It is noticed that replacing THF with DMSO in condition A facilitates deborylation of **3** to yield **4**, and switching from MeCN to DMF in condition B enables further deborylation of **4** to obtain **5**. These two representative phenomena, combined with DFT calculations, help to illustrate the role of solvents.

For deborylation of **3** in THF under condition A (**Fig. C1a**), the energy barrier is as high as 32.3 kcal/mol (**A-Int4→A-TS9**), with the THF-Li coordination existing in **A-Int4**. In DMSO, the energy of **A-Int4-DMSO** and **A-TS9-DMSO** decreases (compared with THF situation), with the latter decreasing even more, resulting in lower deborylation energy barrier of 29.0 kcal/mol (**A-Int4-DMSO→A-TS9-DMSO**). This favors the deborylation of **3** to yield **4**. Under condition B (**Fig. C1b**), Phen-LiOMe is involved in the deborylation of **4**. The corresponding energy barrier is 24.4 kcal/mol in MeCN solvent (**B-Int5→B-TS6"**), whereas it decreased to 23.1 kcal/mol in DMF solvent (**B-TS6"-DMF**), which favors the formation of **5**.

Thus, solvents act through the coordination of important intermediates and the implicit solvent environment, thereby altering the product distribution. The related calculation results and discussions have been added in Supplementary Figure 8. Although we have gained some understanding of the specific role of solvents through experimental and theoretical studies, this is a very complex and systematic problem, and related studies in our laboratory are still in progress.

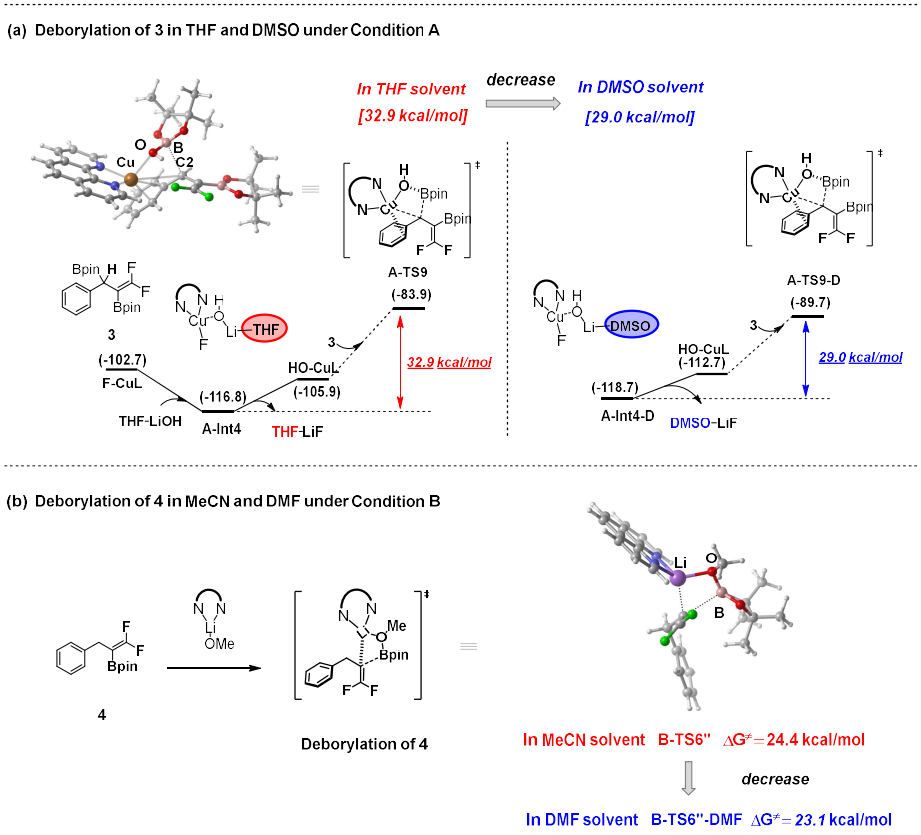


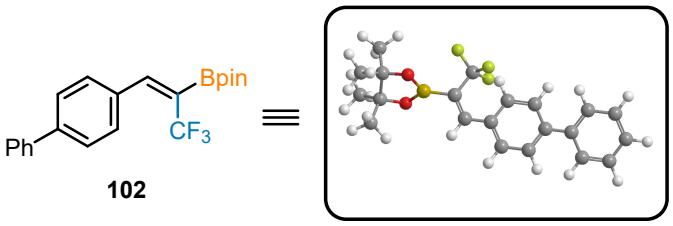
Fig. C1 (a) The comparison between THF and DMSO for deborylation of **3**. (b) The comparison between MeCN and DMF for deborylation of **4**.

3. *"The current form of the mechanistic DFT studies is somewhat crude and riddled with a few issues. And the presentation of the DFT outcomes is rather difficult to follow. To the point that it is distracting from the excellent synthetic work that is performed and reported. The DFT results need a major revision, and they ought to be organized in a manner that is more comprehensible and accessible."*

Response: Following the reviewers' comments, we have carefully revised the DFT calculation section. The detailed free energy curves have been collated in the Supplementary Figure 1-7. The comparison of key transition states that determine selectivity have been placed in the main text (Figure 8). We believe that the current form is clearer and more comprehensible. We would like to thank the reviewer once again for the questions, which allowed us to fundamentally improve the DFT calculation section.

4. *"The stereo configuration (Z/E) of compound 99 depicted in Fig 6 differs from that depicted in Fig 7-9. Assuming the correctness of the stereo configuration presented in Fig 6, it follows that all the mechanistic DFT studies conducted by the authors are erroneous. It is imperative for the authors to thoroughly reevaluate these studies."*

Response: We greatly appreciate the valuable comments. We have revised the stereochemical configuration of compound **102** in the manuscript and confirmed its absolute configuration through X-ray diffraction (XRD) evaluation. The revised *E*-configuration is consistent with the calculation results. (We have renumbered the compounds in the manuscript, changing compound **99** to compound **102**.)



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5. *"There is also a major flaw in the interpretation of the computational results on the regio-selectivity of the Cu–B bond insertion into alkyne substrate 1 (Supplementary Fig5). This process is irreversible, due to its highly exothermic nature. The product stability difference doesn't control the rate of the irreversible reactions. Under the current mechanistic scenario, reverse regio-selectivity would be observed. Compound 100 should be obtained as the major intermediate.*
Additionally, the current Supplementary Fig5 only provides numbers for the free energies of TSs and the intermediates, insights behind the numbers are lacking. It would be critical, if the authors can explain the origin of the difference between the TSs."

Response: We thank the reviewer for the professional comments. We have addressed the regio-selectivity concern, clarified the origin of free energy difference between TSs, and repositioned the crucial content to the main text (Figure 8). These revisions have strengthened the clarity and persuasiveness of the DFT section.

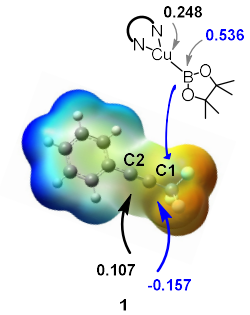


Fig. C2 The NPA charge distribution of substrate **1** and Bpin-CuL.

Based on the natural population analysis (NPA), C1 and C2 atoms of **1**, bonded to -CF_3 and -Ph, exhibit NPA charges of -0.157 and +0.107 (**Fig. C2**). Meanwhile, the Cu and B atoms of Bpin-CuL carry +0.248 and +0.536 charges. The more positive Bpin group should bond with negatively charged C1. However, in our original calculations, the energy barrier of **A-TS1** where Bpin adds to C1 was higher than that of **A-TS1'** where it adds to C2. This inconsistency raised doubts about the effectiveness of the B3LYP-D3/6-311+g**/SDD single-point energy calculation method for this system.

After testing other methods like M06, M06-2X, and M06L that account for dispersion effects, we discovered the energy of **A-TS1** remains higher than **A-TS1'** by 0.90, 0.63, and 0.64 kcal/mol respectively. However, B3LYP without D3 dispersion correction showed reduced difference of only 0.29 kcal/mol. Further removing the dispersion function from the basis set and using 6-311g**, the relative energy barriers of **A-TS1** and **A-TS1'** reversed, with the former being -1.22 kcal/mol lower than the latter. Based on this, we assume that the system may not require extensive consideration of dispersion effects. Therefore, in the revised text, we used B3LYP/6-311g**/SDD for all the single point energy calculation. Based on the revised method, both the regioselectivity of C≡C bond insertion and C=C bond

insertion is consistent with the experimental results, and the product distribution exhibited in conditions A and B can also be properly explained. The overall energy barrier values for Condition A and B are more consistent with the experimental heating temperature of 60 °C.

The explanation for the origin of the difference between the TSs in the original Supplementary Fig. 5 is as follows (**Fig. C3**): Under Condition A, the Cu-Bpin insertion into the C≡C bond of **1** exhibits a lower energy barrier for Bpin addition to C1 atom adjacent to CF_3 (20.5 kcal/mol for **A-TS1**), compared to Bpin addition to C2 atom adjacent to the aryl group (21.7 kcal/mol for **A-TS1'**). The natural population analysis (NPA) charges of **A-TS1** and **A-TS1'** indicate that the more negative charge on C1 favors the attack by the positively charged B atom of -Bpin, therefore the Bpin-C1 bonding is favored. Next, the Cu-Bpin insertion into the C=C bond of **102** shows a lower energy barrier for Bpin addition to C2 atom (24.9 kcal/mol for **A-TS5**), compared to Bpin addition to C1 atom (40.0 kcal/mol for **A-TS5'**). Structural analysis of **A-TS5** and **A-TS5'** indicates the former avoids the significant steric hindrance of two bulky Bpin groups.

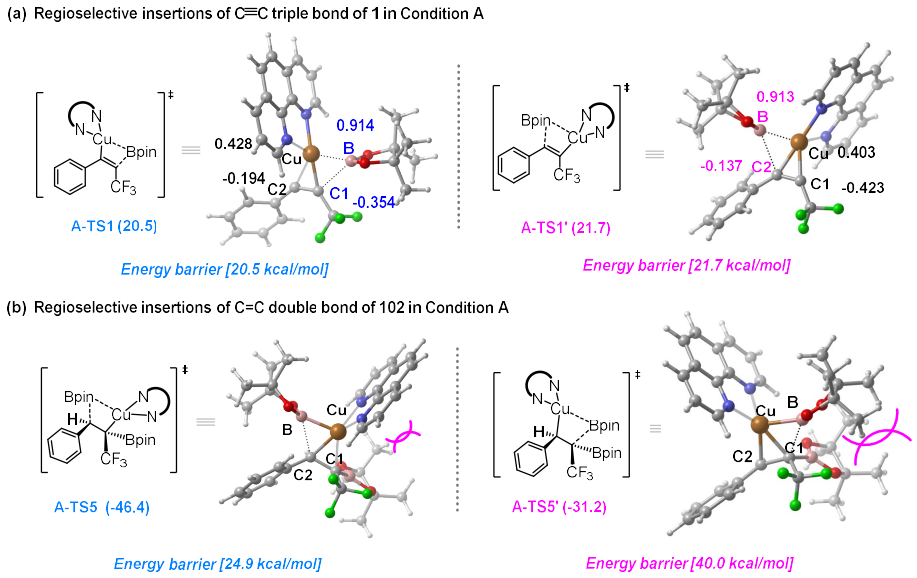


Fig. C3 The regioselective C≡C bond and C=C bond insertion under Condition A.

6. *"As to the calculated profiles, certain steps must be taken into account regarding the transitional state. For instance, in the Supplementary Fig4, the process of the O-H bond broken and the subsequent protonation necessitate a transition state that bridges A_Int1 and A_Int2, as well as a transition state that links A_Int2 to 99. The related calculations should be considered to check the rate-determining step. Moreover, the transition state for the transmetallation of LCu-OMe with B2(pin)2 also need to be calculated. Additionally, it is advisable to substitute Supplementary Figure 4 for Fig. 8 in the main text to mitigate any potential misunderstandings."*

Response: We extend our sincere gratitude to the reviewer for the valuable comments. We have thoroughly revised the protonation process and added the transmetallation transition state between LCu-OMe and $B_2(pin)_2$. These modifications substantially complete the mechanism. For clarity reason, the detailed reaction profiles are moved to Supplementary Figure 1-7.

Regarding the protonation involving two LiOMe molecules in the original version, the proton is unable to approach the C atom sufficiently to establish an effective protonation transition state. Thus, we

explored two alternative mechanisms (**Fig. C4**): 1) Direct H_2O protonation without LiOMe, proceeding via **A-TS2** with an energy barrier of 24.1 kcal/mol. 2) Protonation involving a single LiOMe molecule, progressing through **A-TS3** with an energy barrier of 12.8 kcal/mol, wherein protonation and C-Cu breakage occur concertedly. The latter is more favorable. For the transmetallation between LCu-OMe and $B_2(pin)_2$, we successfully identified the transition state **A-TS4** with a feasible energy barrier of 14.5 kcal/mol.

Accordingly, the revised mechanism seems more reasonable (**Fig. C4**). The olefins insertion is the rate-determining step (**102+Bpin-CuL→A-TS5**), with an overall energy barrier of 24.9 kcal/mol. As mentioned above, compared to the original 15.0 kcal/mol, this energy barrier is more consistent with the experimental reaction temperature of 60 °C.

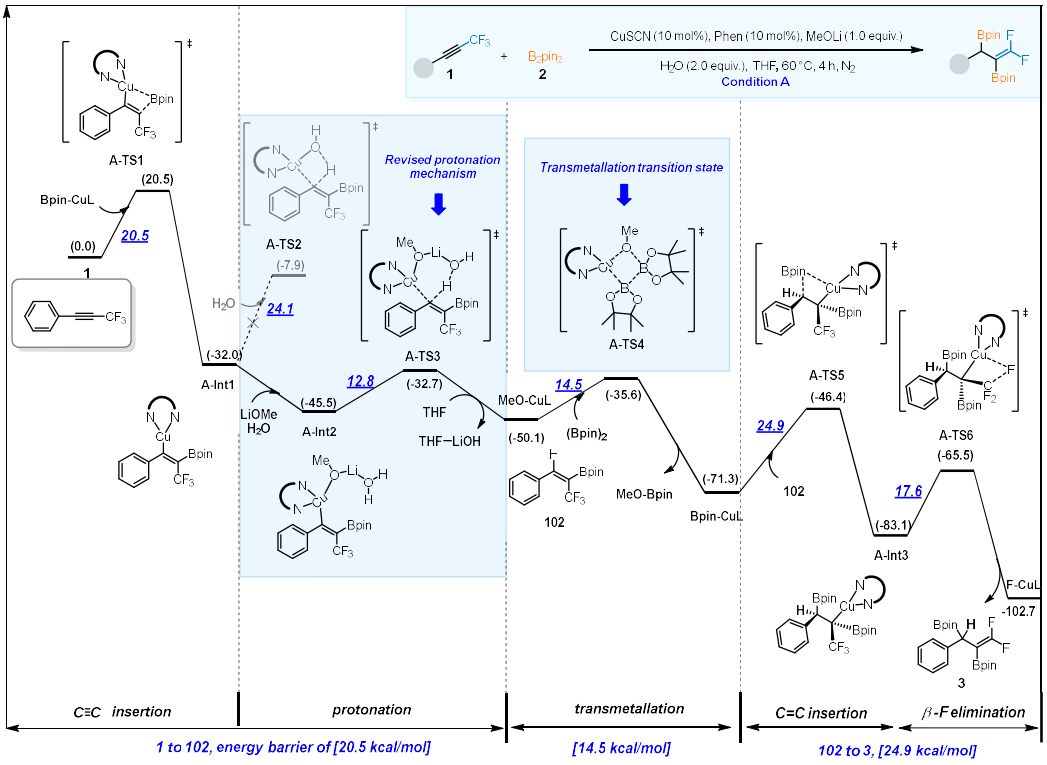


Fig. C4 The calculated Gibbs free energy profiles for the reaction mechanism under Condition A.

7. *"Given that this is an English language journal, the authors need to work with a native-English speaking copy editor to make the manuscript readable to the target audience."*

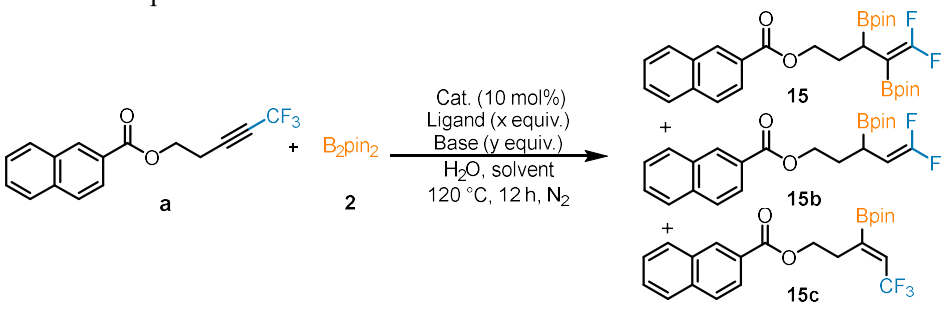
Response: Thanks for the reviewer's suggestions. We've polished the manuscript with the help of a native-English speaking copy editor to make the manuscript readable to the target audience as far we can.

Referee 2:

1. *"XXX reported Cu-catalyzed highly switchable defluoroborylation and hydrodefluorination of trifluoromethylated alkynes, which provides a rare instance of highly selective generation of four kinds of CF2-containing compounds from a single substrate. Synthetically, it is still very novel to start from a single substrate and realize the obtaining of different products by simply changing the conditions of the reaction. However, it is worth pointing out that the present reaction is not very innovative in terms of the mechanism of the reaction in line with the aims of Nat. Commun journal, although the authors tried to illustrate the innovation of the reaction mechanism by means of DFT. Mechanistically, the core intermediate of this reaction is the regioselective addition of Cu-B to trifluoroalkynes in the first step, which leads to a number of subsequent transformations; the continued addition of Cu-B to trifluoromethyl olefins in the later step is a well-known process. And the protonolysis about alkenyl borate is likewise a known reaction. The authors' control experiments also show to some extent that it is possible to obtain the other three products from product 3 without copper catalysts. In addition, the reaction substrates in this paper are still very limited (diborylated scope is only 10). In addition, the reviewer speculates whether alkyl-substituted trifluoromethyl alkynes (e.g., 14 in Fig. 2) could also be used for the expansion of the next three types of products."*

Response: We appreciate the reviewer's valuable suggestion. Firstly, we regretfully acknowledge that we omitted the footnote regarding the reaction conditions for the generation of compound **14** in **Fig. 2** in the previous manuscript. The optimal condition for the diborylation of alkyl-substituted trifluoromethyl alkynes are as follows: **a1** (0.2 mmol), B_2pin_2 **2** (3.0 equiv.), CuSCN (10 mol%), **L1** (10 mol%), MeOLi (3.0 equiv.), and H_2O (2.0 equiv.) in Tolune (2.0 mL) at 120 °C for 12 h under a nitrogen atmosphere.

During the reaction condition optimization, it was observed that predominantly hydroboration product **15c** formed when alkyl-substituted trifluoromethyl alkyne **a** was used as a substrate under conditions A, B, and C (entries 1-3). After careful adjustments to the ligand, base, reaction temperature, solvent, and component ratios, we identified the optimal conditions for the diborylation (entry 4) and subsequent mono-borylation (entry 22) of alkyl-substituted trifluoromethyl alkynes. It is important to note that the Bpin group in mono-borylated product **15b** differ from those in aromatic compound, as the C(sp^3)-Bpin bond reactivity at allyl site is lower than that of alkenyl C(sp^2)-Bpin in alkyl-substituted product. The detailed optimizations are shown below:

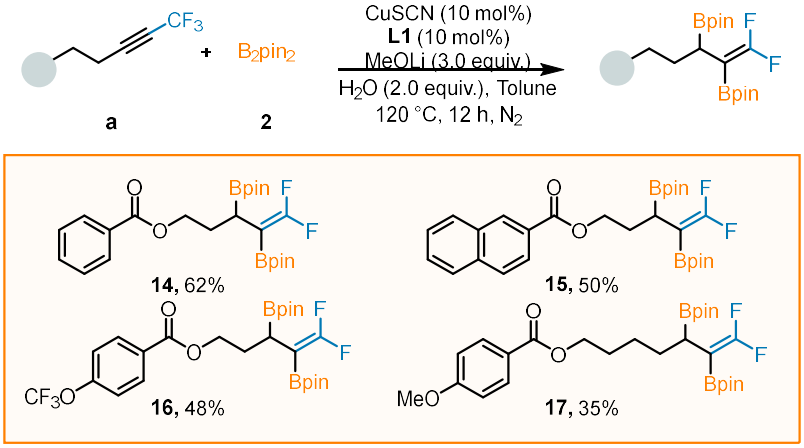


Entry	Cat. (10 mol%)	Ligand (x equiv.)	Base (y equiv.)	Solvent	Yield(%)[a] b	c	d

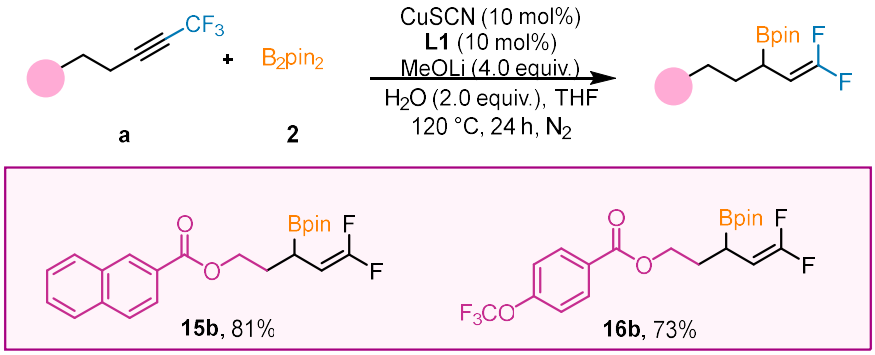
1[b]	CuSCN	Phen (0.1)	MeOLi (1)	THF	trace	trace	95
2[c]	CuSCN	Phen (1.0)	MeOLi (2)	CH_3CN	trace	10	80
3[d]	CuI (20 mol%)	Phen (1.0)	*t*-BuOK (1.5)	DCM	trace	12	85
4	**CuSCN**	**L1 (0.1)**	**MeOLi (3)**	**Tolune**	**50**	**5**	**38**
5	Cu_2O	L1 (0.1)	MeOLi (3)	Tolune	18	0	76
6	CuTC	L1(0.1)	MeOLi (3)	Tolune	10	0	86
7	CuSCN	L2 (0.1)	MeOLi (3)	Tolune	5	10	81
8	CuSCN	L3 (0.1)	MeOLi (3)	Tolune	8	0	90
9	CuSCN	L4 (0.1)	MeOLi (3)	Tolune	14	0	81
10	CuSCN	L5 (0.1)	MeOLi (3)	Tolune	17	0	81
11	CuSCN	L7 (0.1)	MeOLi (3)	Tolune	24	4	67
12	CuSCN	L7 (0.1)	MeOLi (3)	Tolune	25	0	70
13[e]	CuSCN	L1 (0.1)	MeOLi (3)	Tolune	16	trace	78
14[f]	CuSCN	L1 (0.1)	MeOLi (3)	Tolune	31	trace	62
15[g,h]	CuSCN	L1 (0.1)	MeOLi (4)	Tolune	28	4	63
16	CuSCN (30 mol%)	L1 (0.3)	MeOLi (3)	Tolune	35	8	42
17	CuSCN (50 mol%)	L1 (0.5)	MeOLi (3)	Tolune	3	20	73
18	CuSCN	L1 (0.1)	MeOLi (3)	DMSO	37	3	55
19	CuSCN	L1 (0.1)	MeOLi (3)	DCM	22	3	71
20	CuSCN	L1 (0.1)	MeOLi (3)	THF	35	37	22
21[h]	CuSCN	L1 (0.1)	MeOLi (4)	THF	36	45	15
22[g,h]	**CuSCN**	**L1 (0.1)**	**MeOLi (4)**	**THF**	**4**	**81**	**13**
23[e,g,h]	CuSCN	L1 (0.1)	MeOLi (4)	THF	20	64	11
24[f,g,h]	CuSCN	L1 (0.1)	MeOLi (4)	THF	12	71	13
25[e,h]	CuSCN	L1 (0.1)	MeOLi (4)	THF	25	50	21

Unless otherwise specified, the reaction was carried out with **a** (0.2 mmol), **2** (2.0 equiv.), copper catalyst (10 mol%), Ligand (0.1-1.0 equiv.), H_2O (2.0 equiv.) and base (1.0-4.0 equiv.), in solvent (2.0 mL) at 120 °C, 12 h under nitrogen atmosphere. [a]The yield was determined by GC using biphenyl as an internal standard. [b]condition A. [c]condition B. [d] condition C. [e]60 °C. [f]90 °C. [g]Reaction was carried out for 24 h. [h]Using 4.0 equiv. B_2pin_2.

Having established the optimal reaction conditions, we further extended the scopes of alkyl-substituted trifluoromethyl alkynes for the synthesis of di-borylated products and mono-borylated products, and the results were added in **Fig. 2, Fig. 3** and Supplementary Information.



Reaction conditions were: the reaction was carried out with **a** (0.2 mmol), **2** (3.0 equiv.), CuSCN (10 mol%), **L1** (10 mol%), H_2O (2.0 equiv.) and MeOLi (3.0 equiv.), in Tolune (2.0 mL) at 120 °C, 24 h under nitrogen atmosphere.

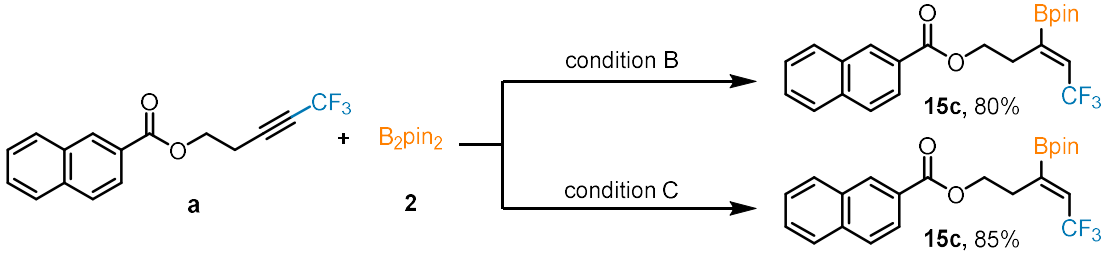


Reaction conditions were: the reaction was carried out with **a** (0.2 mmol), **2** (4.0 equiv.), CuSCN (10 mol%), **L1** (10 mol%), H_2O (2.0 equiv.) and MeOLi (4.0 equiv.), in THF (2.0 mL) at 120 °C, 24 h under nitrogen atmosphere.

Referee 3:

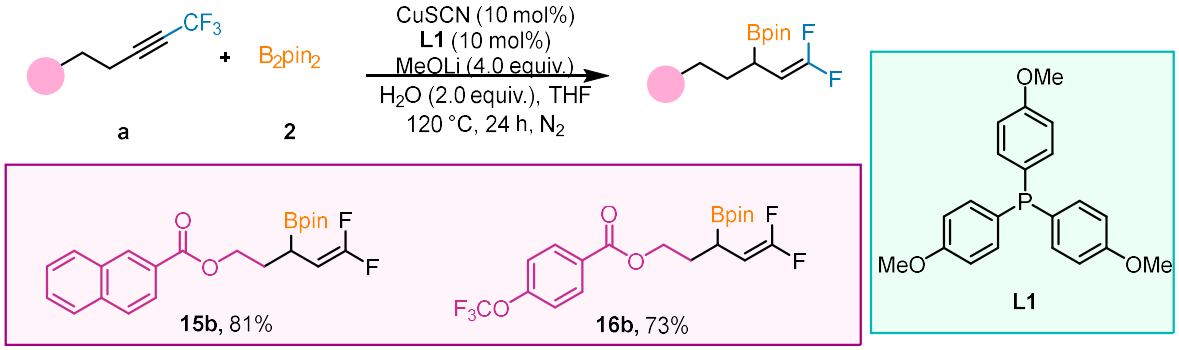
1. *"Recommendation: Publish after major revisions are noted.*
   Comments:
   The authors describe a Copper-Catalyzed Highly Switchable Defluoroborylation and Hydrodefluorination of 1-(Trifluoromethyl) Alkynes to access synthetically challenging CF2-containing compounds in simple and efficient ways. By simply altering the base, hydrodefluorination products of gem-difluoroalkenes or difluoromethylalkenes could also be selectively generated, making the work interesting and valuable to the synthetic community. Though Song and coworkers have already developed a Copper-Catalyzed diborylation of halotrifluoromethyl olefins (ref 36), via a similar strategy involving a beta-fluoride elimination by the copper intermediate. In light of this report, the present work is not entirely novel. A few points need to be addressed before it can be suitable for publication."
   Response: We thank the reviewer for the positive comments.

2. *"Will the reaction work for conditions B and C (Figures 3 and 4) with aliphatic alkynes? The author should show some examples with aliphatic substituents."*
   Response: We appreciate the reviewer's valuable suggestion and tried the reaction for conditions B and C with aliphatic alkynes. Unfortunately, the alkyl-substituted trifluoromethyl alkynes **a1** did not yield the corresponding products under conditions B, and C, only the formation of intermediate **15c** was observed.



Through a series of conditions optimization, we have identified the optimal conditions for generating aliphatic mono-borylated products and provided examples to demonstrate the reaction's generality. It's important to note that the C-B bond sites in these mono-borylated products differ from those in aromatic

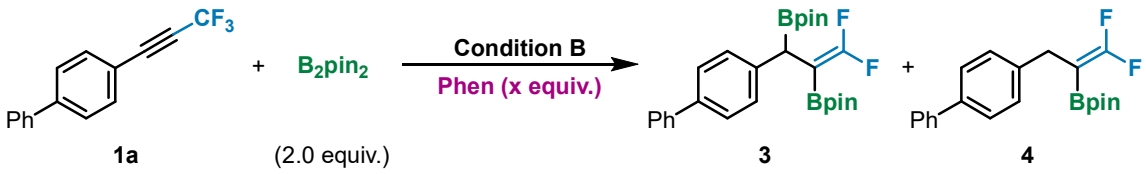
compounds, owing to the C-B bond activity at allyl sites is lower than that of alkenyl C(sp^2)-B bond in alkyl-substituted products.

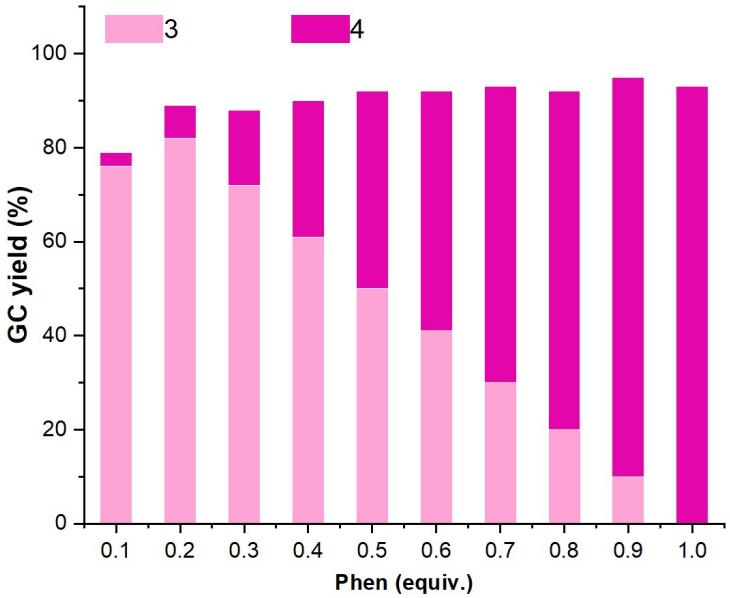


Reaction conditions were: the reaction was carried out with **a** (0.2 mmol), **2** (4.0 equiv.), CuSCN (10 mol%), **L1** (10 mol%), H_2O (2.0 equiv.) and MeOLi (4.0 equiv.), in THF (2.0 mL) at 120 °C, 24 h under nitrogen atmosphere.

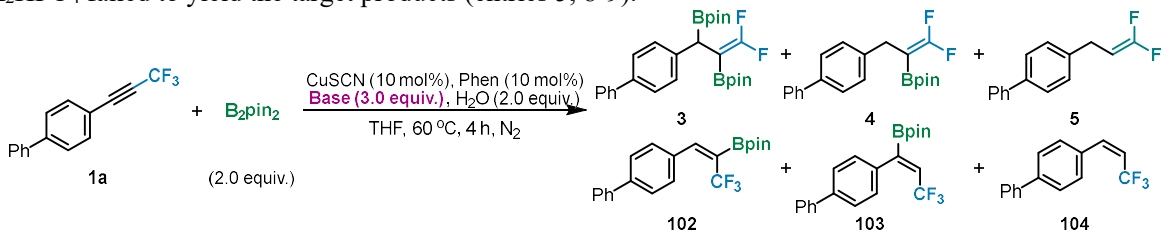
3. *"The requirement of 1 equiv. of Phen in condition B is not clear. The authors must study this carefully. It's hard to imagine why a weak Lewis basic additive would enable such reactivity."*

Response: We appreciate the insightful suggestion from the reviewer. We have investigated the impact of Phen on product selectivity by adding different equivalents of Phen under condition B, and found that as the Phen equivalent increased, the product shifted gradually from **3** to **4**, and a complete transformation occurred at 1 equivalent. This observation underscores the necessity of 1 equiv. of Phen. These results have been incorporated into **section 7.2** of the Supplementary Information.





In addition, we also explored the effects of various bases under catalytic amounts of Phen (10 mol%). We observed that increasing the basicity and quantity of the base indeed promoted further down-conversion of the reaction. However, it proved challenging to control the reaction to halt at specific intermediate stages (entries 1-4, 6, 7). Notably, using K_3PO_4 resulted in high selectivity for mono-borylated products with minimal formation of protonated by-products **104** (entry 10). Conversely, employing KOAc, Pyridine and K_2HPO_4 failed to yield the target products (entries 5, 8-9).



Entry	Base (2.0 equiv.)	Yield(%)[a]						
		3	4	5	102	103	104	1a
1	*t*-BuOK	0	50	3	7	0	18	0
2	CH_3COOCs	28	45	0	0	24	3	0
3	DBU	0	0	40	0	0	43	0
4	*t*-BuOLi	trace	37	46	4	0	4	0
5	CH_3COOK	trace	0	0	16	74	2	7
6	K_2CO_3	trace	23	62	0	0	11	0
7	KF	34	46	0	3	14	0	0
8	Pyridine	trace	0	0	0	0	trace	94
9	K_2HPO_4	trace	0	0	51	7	0	0
10	K_3PO_4	trace	71	0	0	0	20	0

Besides, according to the DFT calculation results, 1 equiv. of Phen-LiOMe species could be obtained from the 1 equiv. of Phen and 2.0 equiv. of LiOMe in Condition B. This species is the key to the deborylation of **3** to produce **4**. As shown in **Fig. C5**, the Phen-LiOMe participated deborylation at the benzyl site of **3** proceeds through **B-TS6** with energy barrier of 21.4 kcal/mol. However, in Condition A, the Phen-LiOMe species is absent. Instead, the Phen-CuOH species participates in the deborylation reaction, encountering a significantly higher energy barrier of 32.3 kcal/mol (**A-TS9**).

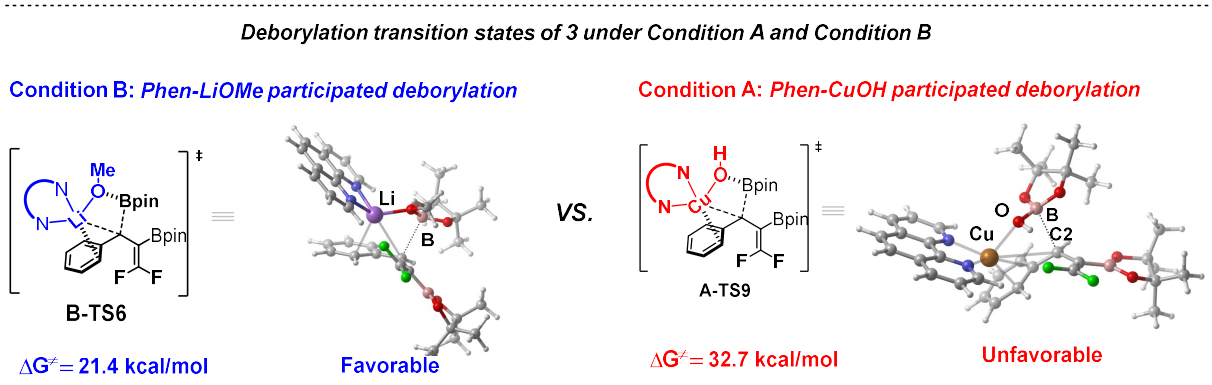


Fig. C5 Deborylation transition states of **3** under Condition A and Condition B

4. *"In the case of Compound 14, What is the reason behind regioselectivity? According to DFT, regioselectivity comes from the aromatic substituent, which is absent in this case. Please comment."*

Response: We appreciate the valuable comments from this reviewer. Firstly, we regretfully acknowledge that we omitted the footnote regarding the reaction conditions for the generation of compound **14** in **Fig. 2** in the previous manuscript. The optimal condition for the formation of aliphatic diborylated products are as follows: alkyl-substituted trifluoromethyl alkyne (0.2 mmol), B_2pin_2 **2** (3.0 equiv.), CuSCN (10 mol%), tris(4-methoxyphenyl)phosphine **L1** (10 mol%), MeOLi (3.0 equiv.), and H_2O (2.0 equiv.) in toluene (2.0 mL) at 120 °C for 12 h under a nitrogen atmosphere.

The regioselectivity of compound **14** is indeed an intriguing issue. We have isolated a hydroborylation by-product from the reaction involving this substrate, which is a result of single borylation with Bpin bonded to C2. DFT calculations indicate that, in the presence of phosphorus ligand (rather than Phen ligand), the energy barrier for **TS1′-14L1**(C2-Bpin bonding) is lower than that for **TS1-14L1** (C1-Bpin bonding) (14.1 vs 20.0 kcal/mol) (**Fig. C6**). Based on this, it is possible that alkyl-substituted trifluoromethyl alkynes undergoes a completely different reaction pathway to yield the similar defluoroborylation product **14** as observed with aromatic substituent substrates. This interesting phenomenon will be another important topic and related research is underway.

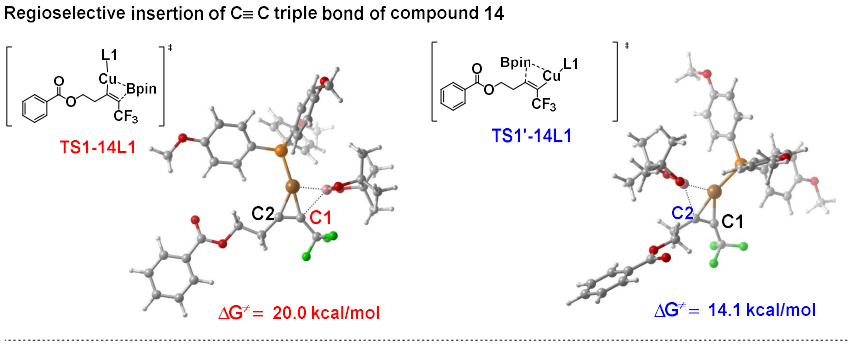


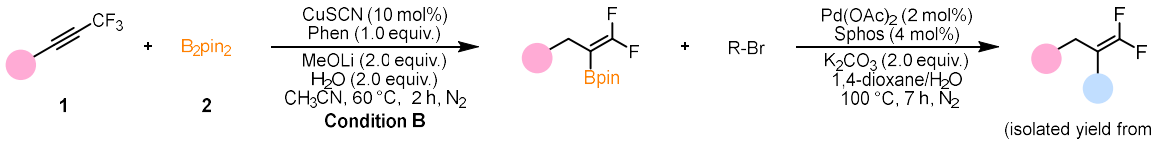
Fig. C6 The calculated C≡C bond insertion transition states for substrate **14**.

5. *"The present method pertaining to Conditions C and D seems highly atom-uneconomical. I don't see any advantage in making these gem-difluoro compounds through this method. Justification on this front is not available in the main text."*

Response: Thank you for your questions. Currently, there are indeed several effective methods available for synthesizing *gem*-difluoroalkenes and difluoromethylated alkenes. For example, the reaction between carbonyl compounds and difluorocarbene precursors is the most commonly used method for synthesizing *gem*-difluoroalkenes. However, this method makes it challenging to synthesize *gem*-difluoroalkenes containing ketone groups, which have significant potential for derivatization. Additionally, the direct difluoromethylation of alkenes or alkenyl halides is an important method for synthesizing difluoromethyl-substituted alkenes. However, these methods are still limited by the need for expensive stoichiometric difluoromethyl reagents or metal catalysts. Therefore, the synthetic methods developed in this work will provide an important alternative strategy for the preparation of both difluoroalkenes and difluoromethyl substituted alkenes. Moreover, the primary advantage of this strategy lies in its capability to establish a unified catalytic system that synthesizes four types of highly adjustable fluorine-containing compounds from a single starting material. A unified system for the selective construction of fluorinated organoboron skeletons with a controllable number of boronate moieties has not been reported so far.

6. *"In the case of Figure 3; after the monoborylation, the reaction mixture was filtered through a short plug of silica gel and washed with DCM as the eluent. Then, a coupling reaction was performed. This reaction is not an in-situ transformation but a two-pot sequential one."*

Response: Thank you for your suggestion. We have removed the term "in situ" from Figure 3 and the corresponding section in the Supporting Information.

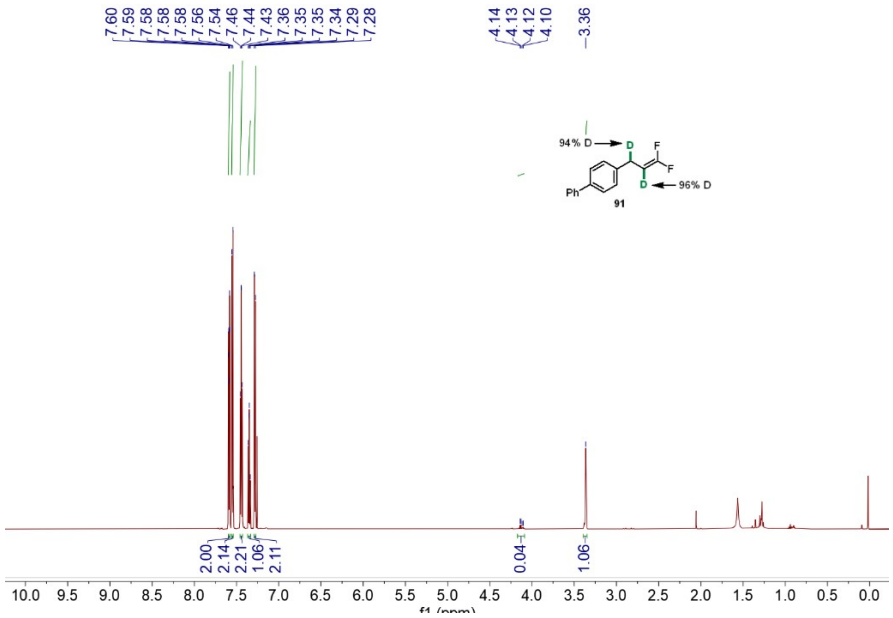


7. *"Some of the compounds are impure. The 13C- peaks, in some cases, are too small (compounds 9, 13, 16, 19, 23, 40, 42, 50, 79, 92). In the case of few compounds, there are unidentified peaks in the 11B spectrum near 20 ppm. These must be addressed before publication."*

Response: We sincerely thank the reviewer for point out this issue. These compounds were further isolated and purified, and the new ^{13}C NMR spectrums of the above compounds (**9, 13, 19, 22, 26, 43, 45, 53, 82 and 95**) have been provided on page S259, S267, S278, S283, S289, S314, S317, S329, S373 and S393 of the SI. The new ^{11}B NMR spectrums of the above compounds (7, 8 and 12) have been provided on page S256, S258 and S266 of the SI. (We have renumbered the compounds in the manuscript, changing compound **16, 19, 23, 40, 42, 50, 79 and 92** to compound **19, 22, 26, 43, 45, 53, 82 and 95**.)

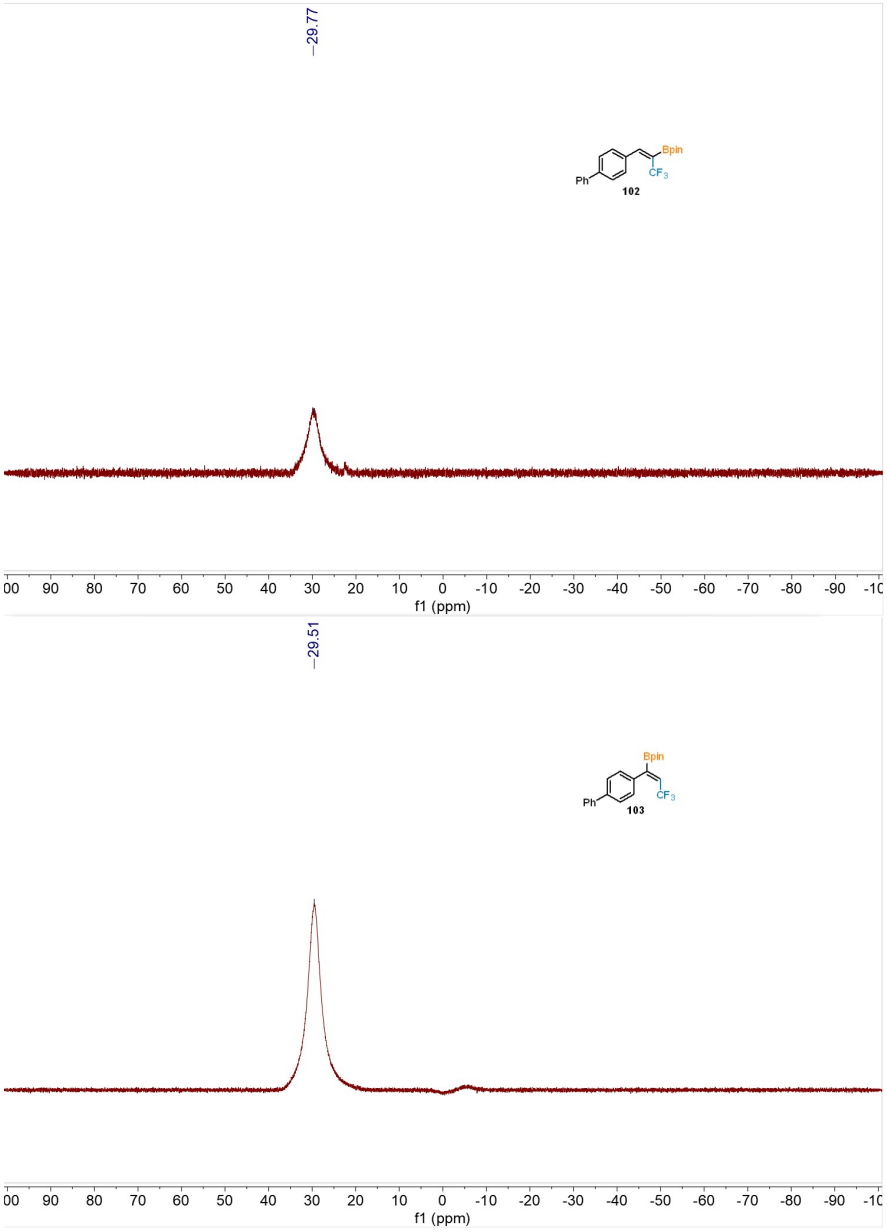
8. *"In the case of Compound 91; the percentage of deuterium incorporation is missing."*

Response: In our resubmitted manuscript, we have incorporated the necessary corrections to the content in **Figure 5**. (We have renumbered the compounds in the manuscript, changing compound **91** to compound **94**.)



9. *"11B is missing for compounds 99 and 100."*

Response: Thanks for the reviewer's suggestions. In our resubmitted manuscript, we have added ^{11}B NMR of compounds **102** and **103 in** the Supporting Information. (We have renumbered the compounds in the manuscript, changing compound **99** and **100** to compound **102** and **103**.)



10. *"Detailed analysis proof for the formation of compound 100 is missing."*

Response: The byproduct compound **103** could be obtained through protonation of **A-Int1'**, an intermediate generated from the unfavorable C2-Bpin bonding transition state **TS1'** (**Fig. C7**). And we

have isolated compound **103** under the condition of Fig. 6 | Mechanistic experiments Aa. (We have renumbered the compounds in the manuscript, changing compound **100** to compound **103**.)

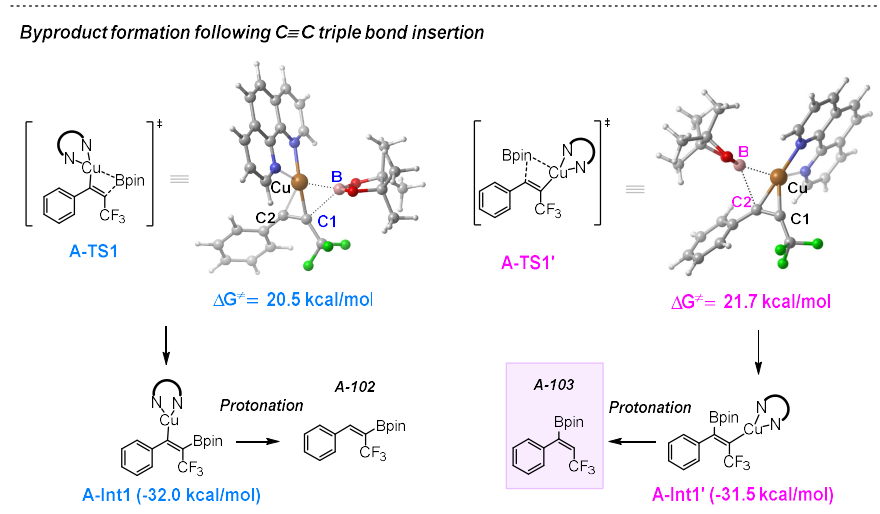
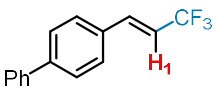


Fig. C7 Byproduct formation following C≡C triple bond insertion.

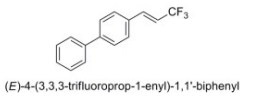
11. *"There is no proof for the other isomerization of compound 101."*

Response: We have determined the absolute configuration of compound **104** to be (*Z*)-4-(3,3,3-trifluoropropenyl)-1,1'-biphenyl by comparing the ^{1}H NMR spectra of **104** with (*E*)-4-(3,3,3-trifluoropropenyl)-1,1'-biphenyl (Reference: *Org. Lett.* **2012**, *14*, 2286–2289.). As shown below, there is a noticeable difference in the chemical shifts of H_1 and H_2 among the different configurations of trifluoromethyl alkenes. (We have renumbered the compounds in the manuscript, changing compound **101** to compound **104**.)

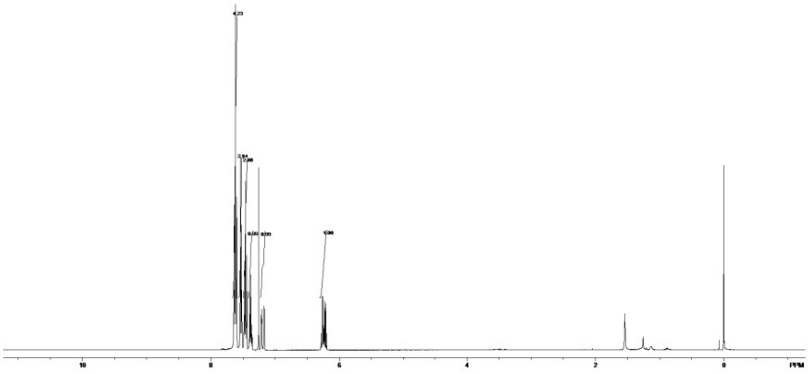


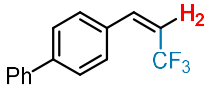
(*E*)-4-(3,3,3-trifluoropropenyl)-1,1'-biphenyl

H_1: 6.24 (dq, J = 16.1 Hz, 6.7 Hz, 1H).



(*E*)-4-(3,3,3-trifluoroprop-1-enyl)-1,1'-biphenyl

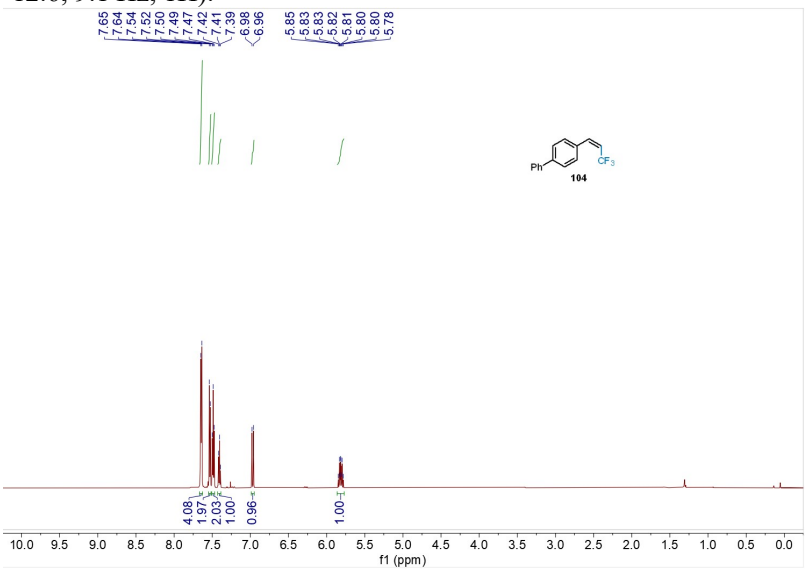




104

(*Z*)-4-(3,3,3-trifluoropropenyl)-1,1'-biphenyl

H_2: 5.81 (dq, J = 12.6, 9.1 Hz, 1H).



12. *"In the case of SI-42, the title page is added again. It must be removed before publication."*

Response: We sincerely appreciate the reviewer for pointing out this issue. In the revised manuscript, the title page for SI-42 has been removed.

13. *"SI: [M+H]+ should be changed to $[M+H]^+$ when writing the HRMS value."*

Response: Thanks for the reviewer's suggestions. In the revised manuscript, we corrected our mistakes.

14. "SI: In the case of page S9, the footnote is missing for the table."

Response: We sincerely thank the reviewer for point out this issue. In the revised manuscript, the footnote has been added.

We wish that the revised manuscript could be acceptable for publication in *Nat. Commun.* Your kind consideration is highly appreciated.

With our best wishes

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors have adequately responded to the reviewers' questions, thus making the manuscript acceptable in its current state.

Reviewer #2 (Remarks to the Author):

The authors provide new substrates for examination and a more detailed description of the mechanism. These additional notes and the revised manuscript make the work reported by XXX on the defluoroboronation of trifluoromethyl-substituted alkynes under different conditions, yielding varying degrees of reactivity and products, appear more detailed and meaningful. I consider the work suitable for publication in Nat Commun.

Reviewer #3 (Remarks to the Author):

The revision submitted by the authors has satisfactorily addressed the queries of the reviewers. The additional experiments performed by the authors support their observations. The manuscript may be accepted in the present form.