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Copper-Catalyzed Carboxylation of C-F Bonds with CO₂

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ABSTRACT: An effective Cu-catalyzed selective formal carboxylation of C–F bonds with an atmospheric pressure of CO₂ is reported. A variety of *gem*-difluoroalkenes, *gem*-difluorodienes and α -trifluoro-methyl alkenes show high reactivity and selectivity for this *ipso* mono-carboxylation. Under mild conditions, diverse important α -fluoroacrylic acids and α, α -difluorocarboxylates are obtained in good-to-high yields. Moreover, this operationally-simple protocol features good functional group tolerance, is readily scalable, and the resulting products are readily converted into bioactive α -fluorinated carbonyl compounds, indicating potential application in biochemistry and drug discovery. Mechanistic studies reveal that fluorinated boronate esters might be vital intermediates in this transformation.

KEYWORDS: carbon dioxide, carboxylation, C-F bond cleavage, selectivity, copper catalysis

As an inexpensive and renewable carbon source, CO_2 has been widely used in organic synthesis to make value-added chemicals.1 Among these transformations, catalytic carboxylation with CO₂ is well demonstrated to construct valuable carboxylic acids,² which is a functional group that exists widely in natural products, agrochemicals and pharmaceuticals.³ Recently, the reductive carboxylation of organic (pseudo)halides with CO₂ has been extensively studied,^{4,5} presenting powerful and efficient alternatives to existing carboxylation methods with organometallic reagents.^{2,6} Notably, the catalytic carboxylation of diverse C-X bonds (X = Cl, Br, I, O, N) in the presence of reductants is well documented using different transition metal catalysts (Figure 1A).^{4,5} However, the transition metal-catalyzed formal carboxylation of C-F bonds with CO₂ is considered challenging and has been rarely investigated.7 This is reasonable due to the low reactivity of CO₂ and exceptional inertness of C-F bonds, which show much higher bond dissociation energy and are less reactive toward oxidative addition to low-valent transition metal catalyst than other C-X bonds.8 Therefore, a novel strategy should be considered to address such a challenge. Herein, we report the first coppercatalyzed selective formal carboxylation of C-F bonds with CO_2 (Figure 1B). A variety of valuable α -fluoroacrylic acids and α, α -difluorocarboxylates are obtained in high selectivities and efficiency using inexpensive catalyst and non-metallic reductants.

 α -Fluoroacrylic acids are important motifs widely present in medicines and bioactive molecules (Figure 2).⁹ Previous methods for their synthesis suffer, however, from tedious procedures, limited substrate scope, poor functional group tolerance, and low selectivity or yield.^{9b,10} Moreover, some expensive reagents are usually required, thus limiting applicability. Since selective functionalization of C–F bonds in easily available multifluorinated compounds provides an alternative access to complex partially fluorinated molecules,¹¹⁻¹⁴ we wondered whether selective carboxylation of C–F bonds in *gem*-difluoroalkenes¹³ with CO₂ could constitute a direct and efficient entry to α -fluoroacrylic acids. Realizing this hypothesis, however, suffers several challenges. Besides the above-mentioned inertness of both C–F bonds and CO₂, it is also challenging to realize selective mono- instead of di-carboxylation of C–F bonds in *gem*-difluoroalkenes due to their similar bond energies.

(A) Previous carboxylation of C-X bonds with CO_2		
	cat. Ni or Pd or Cu	

	00	ligand	D-00 II
R-X +	CO_2	reductant	к-со2п
X = CI, Br, I, OR^1 , $MMe_3\overline{X}$	(1-10 atm)	(Mn, Zn, Et ₂ Zn,)	

(B) Copper-catalyzed selective carboxylation of C-F bonds with CO₂ (This work)

R _f —F	+	+ CO ₂ (1 atm)	cat. Cu/L	
	т		(B(OR) ₂) ₂	Rf [−] CU ₂ H

+ High selectivity + Good FG tolerance + Important and diverse + Mild conditions + Broad substrate scope + Easy derivation

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Challenges: low reactivity (C-F cleavage and CO<sub>2</sub> activation) selectivity (mono-, regio- and stereo-selectivities)
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Figure 2. Selected bioactive α -fluoroacrylates and derivatives.

As direct carboxylation of C–F bonds with CO₂ is difficult via oxidative addition, we wondered whether we could realize the C–F bond cleavage via β -F elimination^{13,14} and generate

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reactive organometallic reagents, which might react with CO₂ under mild reaction conditions. We began our investigations by evaluating the reaction of 4-(2,2-difluorovinyl)-1,1'biphenyl (1a) with CO_2 and a copper(I)/diboron catalytic system (Table 1). When we conducted the reaction using KOAc or CsF as base, no or only trace amounts of the desired product 2a was detected (entries 1-2). We suspected that a stronger base may be essential to activate the diboron reagents and promote this transformation. Further screening of several strong bases revealed that LiO'Bu afforded 2a in the highest vield (entries 3-5). We also tested other cuprous catalysts and found that CuTc gave the best result (entries 3, 6 and 7). Other solvents, such as DMAc and o-xylene, all resulted in lower yields (entries 8-9). The Xantphos was found to be the best ligand and the B₂pin₂ was the diboron sources of choice (Please see SI for details). Control experiments showed that both the copper catalyst and base were vital to this transformation (entries 10-11). Notably, this formal carboxylation proceeded with high efficiency (entry 12. Please see SI for details) and high (Z)-selectivity; no (E)-isomer was detected by ¹⁹F NMR.

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Table 1. Optimization of the Reaction Conditions^a

$\begin{array}{c} [Cu] \ (5 \ mol\%) \\ Xantphos \ (5 \ mol\%) \\ base \ (3.5 \ equiv) \\ B_2pin_2 \ (1.5 \ equiv) \\ solvent, \ 80 \ ^{\circ}C, \ 24 \ h \\ then \ HCl \ (aq.) \end{array} \begin{array}{c} CO_2 H \\ F \end{array}$					
1a	(1 atm	, closed)		2a	
entry	[Cu]	base	solvent	Yield of 2a (%) ^b	
1	CuTc	KOAc	DMF	N.D.	
2	CuTc	CsF	DMF	trace	
3	CuTc	LiO ^t Bu	DMF	88 (85)	
4	CuTc	NaO ^t Bu	DMF	59	
5	CuTc	KO ^t Bu	DMF	44	
6	Cul	LiO ^t Bu	DMF	73	
7	CuOAc	LiO ^t Bu	DMF	83	
8	CuTc	LiO ^t Bu	DMAc	70	
9	CuTc	LiO ^t Bu	o-xylene	65	
10	-	LiO ^t Bu	DMF	N.D.	
11	CuTc	-	DMF	N.D.	
12 ^c	CuTc	LiO ^t Bu	DMF	85	

^aReaction conditions: **1a** (0.4 mmol), 1 atm of CO₂, [Cu] (0.02 mmol), Xantphos (0.02 mmol), base (1.4 mmol), B₂pin₂ (0.6 mmol), solvent (2 mL), 80 °C, 24 h. ^bYields were determined by UPLC using anisole as an internal standard, and the isolated yields are given in parentheses. ^c2 h instead of 24 h. CuTc = copper(I) thiophene-2-carboxylate. N.D. = not detected. DMF = N,N-dimethylformamide. DMAc = N,N-dimethylacetamide.

The best reaction conditions were used for further evaluation of the scope of gem-difluoroalkenes (Scheme 1). Substrates bearing either an electron-donating group (EDG) (2e-2h, 2l, 2s and 2x) or an electron-withdrawing group (EWG) (2m-2q and 2u) on the phenyl ring showed good reactivity and gave the carboxylated products 2 in moderateto-high yields. Substituents at different positions on the arenes, such as the para-, meta- and ortho-positions, did not inhibit the reaction. It is worth noting that a variety of synthetically valuable functional groups, including ether (2f, 2g, 2h, 2s and 2x), fluoro (2i, 2v and 2aa), chloro (2j and 2t), bromo (2k), amino (21), and sulfone (2p), were all tolerated, providing opportunities for subsequent useful transformations. Moreover, some base-sensitive functional groups, such as methyl ester (2n) and nitrile (2o and 2u), could remain intact under our reaction conditions. Naphthalenes (2y and 2z) and

heterocycles, such as pyridine (2q), benzothiophene (2ab), and quinoline (2ac), were also compatible with this reaction. Interestingly, the reaction of substrate 1ad bearing both an aliphatic and an aryl gem-difluoroalkene provided the single product 2ad in a satisfactory yield, demonstrating the high selectivity of this reaction and acceptable toleration of aliphatic gem-difluoroalkenes. Importantly, the more challenging gem-difluorodienes were also applicable (Scheme 2), affording the desired products 2ae-2ah with high chemoand stereoselectivity, thus significantly extending the scope of the reaction.

Scheme 1. Substrate Scope of gem-Difluoroalkenes^a



^{*a*}Reaction conditions are shown in Table 1, entry 3. ^{*b*}36 h. ^{*c*}CuTc (10 mol%) and Xantphos (10 mol%) were used. ^{*d*}Isolated yields of methyl ester using MeI as esterification reagent.

Scheme 2. Substrate Scope of gem-Difluorodienes^a



^{*a*}Reaction conditions are shown in Table 1, entry 3. ^{*b*}The Z/E ratio was determined by ¹⁹F NMR analysis of reaction mixture. ^{*c*}CuTc (10 mol%) and Xantphos (10 mol%) were used, 36 h.

After realizing the selective carboxylation of $C(sp^2)$ –F bonds in *gem*-difluoroalkenes, we wondered whether we could apply this catalytic system to realize a selective defluorinative carboxylation of $C(sp^3)$ –F bonds in α -trifluoromethyl alkenes¹⁴ with CO₂. The aliphatic C–F bond is well-known to be highly unreactive due to the high BDE of a $C(sp^3)$ –F bond. Moreover, it is rather difficult to avoid multiple defluorinations and thus realize a selective monocarboxylation, since the C–F bonds in the initial products might be activated by the carboxyl group.

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With these challenges in mind, we investigated the carboxylation of trifluoromethyl alkene 3a with CO₂. To our delight, we found that 3a underwent a highly selective ipsocarboxylation of one C-F bond to give the α,α difluorocarboxylate 4a in 70% yield under slightly modified reaction conditions (Scheme 3). Bis(hexylene glycolato)diboron turned out to be a better choice for this case with better yields than B₂pin₂ (Please see SI for details). Notably, this represents a rare example for an ipsofunctionalization of a C-F bond in α -trifluoromethyl alkenes.¹⁵ Although gem-difluoroalkenes typically are obtained via $S_N 2$ '-type reactions in most cases,¹⁴ the formation of isomer 4a' was not observed in our reaction. Importantly, the generated difluoromethylene group (CF₂) at benzylic position has good metabolic stability, which is often regarded as the bioisosteres of oxygen atom, carbonyl group and methylene group,16 thus providing a possibility for the application of the product 4 in medicine and bioactive molecules. Furthermore, the substrate scope of 3 was investigated (Scheme 3). For example, the substrates with different substituents on the arenes, including methoxy (4b, 4g), chloro (4c, 4h, 4o), bromo (4d), and trifluoromethyl (4f) were tested and they afforded the desired α,α difluorocarboxylates in moderate-to-good yields. Besides the substrates bearing monosubstituted benzenes, those with disubstitutions (4j, 4k, and 4m) could also react well to furnish the products effectively. The substrates bearing naphthalene (4l and 4n) or fluorene (4p) also showed good reactivity in this transformation. Notably, multiple defluorinations were not observed in all cases.¹⁷

Scheme 3. Substrate Scope of α-Trifluoromethyl Alkenes^a



^{*a*}Reaction conditions: **3** (0.2 mmol), 1 atm of CO₂, CuCl (0.02 mmol), Xantphos (0.02 mmol), KOMe (0.6 mmol), (B(OR¹)₂)₂ (0.3 mmol), NMP (2 mL), 80 °C, 24 h; isolated yields. (B(OR¹)₂)₂ = Bis(hexylene glycolato)diboron.

To further demonstrate the utility of this transformation, we conducted a gram-scale reaction of **11** to synthesize **21** in 78% yield (Figure 3A. See SI for details). Moreover, products could be readily converted into valuable compounds (Figure 3B. See SI for details). For example, the methyl ester **2a**" readily underwent either reduction to generate fluoroallyl alcohol **5** or [3+2] cycloaddition with an azomethine ylide to give fluoro-

pyrrolidine 6 in one step.¹⁸ Notably, the facile condensation of **2b** with amines gave direct access to bioactive compounds, including anticonvulsant agent 7 (Figure 2) and quinuclidine acrylamide **8**, which can be used for the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders.^{9a,d}

To shed light on the mechanism of this transformation, several experiments were conducted (Figure 4). As we detected the Z-fluorinated vinylboronate ester 9a in the reaction of 1a under the N₂ atmosphere, we speculated that 9a might be the intermediate of the reaction. So we synthesized 9a according to the literature via Cu-catalyzed stereoselective borylation of gem-difluoroalkenes with B2pin2.13f,13h When it was subjected to the carboxylation reaction, the desired product 2a was obtained in 79% yield in 0.5 hour (Figure 4A). Surprisingly, the carboxylation of 9a also proceeded in the absence of a Cu-catalyst (Figure 4B), albeit with a lower efficiency than with Cu-catalysis (Figure 4A). Moreover, preliminary kinetic studies indicated that the Cu-catalysis should dominate the carboxylation of fluorinated vinylboronate ester with CO2 (See SI for details). In order to explain the unusual results in Figure 4B, we further studied the carboxylations of 9b and 9c in the same conditions (Figure 4C). The results indicated that the electron-withdrawing effect of α -substitutions could activate the vinylboronate ester.



Figure 3. Gram-scale synthesis and synthetic applications of products.



Figure 4. Control experiments.

Based on the experimental results and previous reports,¹⁹ we proposed the following possible mechanism for the carboxylation of 1 (Figure 5). Copper(I) alkoxide A would easily undergo transmetalation with the diboron reagent to

afford the boryl-copper(I) species **B**. Subsequently, insertion of a difluoroalkene 1 into the Cu-B bond of B would result in the formation of intermediate C. Among different configurations (C, C' and C''), the steric repulsion between the bulky boryl group and the R group in C" makes it unstable. Thus, syn β -F elimination via C' selectively affords the (Z)-fluorinated pinacol alkenylboronate D and a Cu(I)-F species. In path A, a subsequent Cu(I)-catalyzed transmetallation/carboxylation process would give the desired product 2 and regenerate the active catalyst A. As demonstrated, the direct carboxylation of **D** with CO_2 (path B) might also happen in the presence of LiO'Bu, even though this is less efficient than path A and less favored in the reaction mixture. Another possible pathway to directly generate E from 1 and **B** via a sigma bond metathesis can not be excluded at this stage.



Figure 5. Proposed mechanism.

In conclusion, we have realized the first Cu-catalyzed highly selective formal *ipso*-carboxylation of C–F bonds in fluorinated alkenes with CO₂. A variety of valuable α -fluoroacrylic acids and α, α -difluorocarboxylates, which exist among many drugs but are otherwise difficult to access, were obtained in good yields under mild conditions. Diverse functional groups were well tolerated in the presence of nonmetallic reductants. This method displays inexpensive catalyst, broad substrate scope, high mono-, chemo- and stereo-selectivities, scalability, and rapid access to bioactive molecules, providing great potential for application in organic synthesis, biochemistry and drug discovery.

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ConflictofInterestA Chinese Patent on this work has been applied with the number
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ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic data and copies of NMR spectra for all products are available free of charge via the Internet

at http://pubs.acs.org.

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REFERENCES

(1) Aresta, M. Carbon Dioxide as Chemical Feedstock; Wiley-VCH, Weinheim, **2010**.

(2) For selected reviews, see: (a) Huang, K.; Sun, C.-L.; Shi, Z.-J. Transition-Metal-Catalyzed C-C Bond Formation through the Fixation of Carbon Dioxide. Chem. Soc. Rev. 2011, 40, 2435-2452. (b) Martin, R.; Kleij, A. W. Myth or Reality? Fixation of Carbon Dioxide into Complex Organic Matter under Mild Conditions. ChemSusChem 2011, 4, 1259–1263. (c) Tsuji, Y.; Fujihara, T. Carbon Dioxide as a Carbon Source in Organic Transformation: Carbon-Carbon Bond Forming Reactions by Transition-Metal Catalysts. Chem. Commun. 2012, 48, 9956–9964. (d) Zhang, L.; Hou, Z. N-Heterocyclic Carbene (NHC)-Copper-Catalysed Transformations of Carbon Dioxide. Chem. Sci. 2013, 4, 3395-3403. (e) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. Using Carbon Dioxide as a Building Block in Organic Synthesis. Nat. Commun. 2015, 6, 5933-5947. (f) Yu, D.; Teong, S. P.; Zhang, Y. Transition Metal Complex Catalyzed Carboxylation Reactions with CO2. Coord. Chem. Rev. 2015, 293-294, 279-291. (g) Börjesson, M.; Moragas, T.; Gallego, D.; Martin, R. Metal-Catalyzed Carboxylation of Organic (Pseudo) halides with CO2. ACS Catal. 2016, 6, 6739-6749. (h) Song, Q.-W.; Zhou, Z.-H.; He, L.-N. Efficient, Selective and Sustainable Catalysis of Carbon Dioxide. Green Chem. 2017, 19, 3707-3728. (i) Luo, J.; Larrosa, I. C-H Carboxylation of Aromatic Compounds through CO₂ Fixation. ChemSusChem 2017, 10, 3317-3332. (j) Tortajada, A.; Juliá-Hernández, F.; Börjesson, M.; Moragas, T.; Martin, R. Transition-Metal-Catalyzed Carboxylation Reactions with Carbon Dioxide. Angew. Chem., Int. Ed. 2018, 57, 15948-15982. (k) Yan, S.-S.; Fu, Q.; Liao, L.-L.; Sun, G.-Q.; Ye, J.-H.; Gong, L.; Bo-Xue, Y.-Z.; Yu, D.-G. Transition Metal-Catalyzed Carboxylation of Unsaturated Substrates with CO2. Coord. Chem. Rev. 2018, 374, 439-463. (1) Chen, Y.-G; Xu, X.-T.; Zhang, K.; Li, Y.-Q.; Zhang, L.-P.; Fang, P.; Mei, T.-S. Transition-Metal-Catalyzed Carboxylation of Organic Halides and Their Surrogates with Carbon Dioxide. Synthesis 2018, 50, 35–48. (m) Yeung, C. S. Photoredox Catalysis as a Strategy for CO₂ Incorporation: Direct Access to Carboxylic Acids from a Renewable Feedstock. Angew. Chem., Int. Ed. 2019, 58, 5492-5502. (3) Maag, H. Prodrugs of Carboxylic Acids, Springer: New York, 2007

(4) For Ni-catalysis, see: (a) Fujihara, T.: Nogi, K.: Xu, T.: Terao, J.: Tsuji, Y. Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide. J. Am. Chem. Soc. 2012, 134, 9106-9109. (b) León, T.; Correa, A.; Martin, R. Ni-Catalyzed Direct Carboxylation of Benzyl Halides with CO₂. J. Am. Chem. Soc. 2013, 135, 1221-1224. (c) Correa, A.; León, T.; Martin, R. Ni-Catalyzed Carboxylation of C(sp²)- and C(sp³)-O Bonds with CO₂. J. Am. Chem. Soc. 2014, 136, 1062-1069. (d) Liu, Y.; Cornella, J.; Martin, R. Ni-Catalyzed Carboxylation of Unactivated Primary Alkyl Bromides and Sulfonates with CO2. J. Am. Chem. Soc. 2014, 136, 11212-11215. (e) Moragas, T.; Cornella, J.; Martin, R. Ligand-Controlled Regiodivergent Ni-Catalyzed Reductive Carboxylation of Allyl Esters with CO2. J. Am. Chem. Soc. 2014, 136, 17702-17705. (f) Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Cobalt- and Nickel-Catalyzed Carboxylation of Alkenyl and Sterically Hindered Aryl Triflates Utilizing CO2. J. Org. Chem. 2015, 80, 11618-11623. (g) Wang, X.; Y.; Liu, Martin, R. Ni-Catalyzed Divergent

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Cyclization/Carboxylation of Unactivated Primary and Secondary Alkyl Halides with CO2. J. Am. Chem. Soc. 2015, 137, 6476-6479. (h) Moragas, T.; Gaydou, M.; Martin, R. Nickel-Catalyzed Carboxylation 2 of Benzylic C-N Bonds with CO2. Angew. Chem., Int. Ed. 2016, 55, 5053-5057. (i) Börjesson, M.; Moragas, T.; Martin, R. Ni-Catalyzed Carboxylation of Unactivated Alkyl Chlorides with CO2. J. Am. Chem. Soc. 2016, 138, 7504-7507. (j) Rebih, F.; Andreini, M.; Moncomble, A.; Harrison-Marchand, A.; Maddaluno, J.; Durandetti, M. Direct 6 Carboxylation of Aryl Tosylates by CO₂ Catalyzed by In situ-Generated Ni⁰. Chem. - Eur. J. 2016, 22, 3758-3763. (k) Juliá-8 Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. Remote 9 Carboxylation of Halogenated Aliphatic Hydrocarbons with Carbon Dioxide. Nature 2017, 545, 84-88. (1) Chen, Y.-G.; Shuai, B.; Ma, C.; 10 Zhang, X.-J.; Fang, P.; Mei, T.-S. Regioselective Ni-Catalyzed 11 Carboxylation of Allylic and Propargylic Alcohols with Carbon 12 Dioxide. Org. Lett. 2017, 19, 2969-2972. (m) van Gemmeren, M.; 13 Börjesson, M.; Tortajada, A.; Sun, S.-Z.; Okura, K.; Martin, R. Switchable Site-Selective Catalytic Carboxylation of Allylic Alcohols 14 with CO2. Angew. Chem., Int. Ed. 2017, 56, 6558-6562. (n) Meng, 15 Q.-Y.; Wang, S.; König, B. Carboxylation of Aromatic and Aliphatic 16 Bromides and Triflates with CO2 by Dual Visible-Light-Nickel 17 Catalysis. Angew. Chem., Int. Ed. 2017, 56, 13426-13430.

- 18 (5) For other transition metal catalysis, see: (a) Correa, A.; Martin, R. Palladium-Catalyzed Direct Carboxylation of Aryl Bromides with 19 Carbon Dioxide. J. Am. Chem. Soc. 2009, 131, 15974-15975. (b) 20 Tran-Vu, H.; Daugulis, O. Copper-Catalyzed Carboxylation of Aryl 21 Iodides with Carbon Dioxide. ACS Catal. 2013, 3, 2417-2420. (c) 22 Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Cobalt-Catalyzed 23 Carboxylation of Propargyl Acetates with Carbon Dioxide. Chem. Commun. 2014, 50, 13052-13055. (d) Zhang, S.; Chen, W.-Q.; Yu, 24 A.; He, L.-N. Palladium-Catalyzed Carboxylation of Benzyl 25 Chlorides with Atmospheric Carbon Dioxide in Combination with 26 Manganese/Magnesium Chloride. ChemCatChem 2015, 7, 3972-3977. 27 (e) Mita, T.; Higuchi, Y.; Sato, Y. Highly Regioselective Palladium-Catalyzed Carboxylation of Allylic Alcohols with CO2. Chem. - Eur. 28 J. 2015, 21, 16391-16394. (f) Shimomaki, K.; Murata, K.; Martin, R.; 29 Iwasawa, N. Visible-Light-Driven Carboxylation of Aryl Halides by 30 the Combined Use of Palladium and Photoredox Catalysts. J. Am. 31 Chem. Soc. 2017, 139, 9467-9470. (g) Jiao, K.-J.; Li, Z.-M.; Xu, X.-T.; Zhang, L.-P.; Li, Y.-Q.; Zhang, K.; Mei, T.-S. Palladium-32 Catalyzed Reductive Electrocarboxylation of Allyl Esters with 33 Carbon Dioxide. Org. Chem. Front. 2018, 5, 2244-2248.
- 34 (6) For an elegant review, see: (a) Correa, A.; Martin, R. Metal-35 Catalyzed Carboxylation of Organometallic Reagents with Carbon Dioxide. Angew. Chem. Int. Ed. 2009, 48, 6201-6204. For selected 36 examples, see: (b) Shi, M.; Nicholas, K. M. Palladium-Catalyzed 37 Carboxylation of Allyl Stannanes. J. Am. Chem. Soc. 1997, 119, 38 5057-5058. (c) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. 39 Rhodium(I)-Catalyzed Carboxylation of Aryl- and Alkenylboronic 40 Esters with CO2. J. Am. Chem. Soc. 2006, 128, 8706-8707. (d) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. Nickel-41 Catalyzed Carboxylation of Organozinc Reagents with CO2. Org. Lett. 42 2008, 10, 2681–2683. (e) Yeung, C. S.; Dong, V. M. Beyond Aresta's 43 Complex: Ni- and Pd-Catalyzed Organozinc Coupling with CO2. J. 44 Am. Chem. Soc. 2008, 130, 7826-7827. (f) Ohishi, T.; Nishiura, M.; Hou, Z. Carboxylation of Organoboronic Esters Catalyzed by N-45 Heterocyclic Carbene Copper(I) Complexes. Angew. Chem. Int. Ed. 46 2008, 47, 5792-5795. (g) Duong, H. A.; Huleatt, P. B.; Tan, Q. W.; 47 Shuying, E. L. Regioselective Copper-Catalyzed Carboxylation of 48 Allylboronates with Carbon Dioxide. Org. Lett. 2013, 15, 4034-4037. (h) Makida, Y.; Marelli, E.; Slawin, A. M. Z.; Nolan, S. P. Nickel-49 Catalysed Carboxylation of Organoboronates. Chem. Commun. 2014, 50 50, 8010-8013.

51 (7) During the preparation of this paper, Feng and co-workers 52 reported an elegant carboxylation of C-F bond in gem-53 difluoroalkenes via photoredox/Pd dual catalysis, see: Zhu, C.; Zhang, Y.-F.; Liu, Z.-Y.; Zhou, L.; Liu, H.; Feng, C. Selective C-F Bond 54 Carboxylation of gem-Difluoroalkenes with CO₂ bv 55

Photoredox/Palladium Dual Catalysis. Chem. Sci., 2019, DOI: 10.1039/C9SC01336A. However, the *ipso*-carboxylation of α trifluoromethyl alkenes and gem-difluorodienes with CO2 has never been reported.

(8) (a) Luo, Y.-R. Handbook of Bond Dissociation Energies in Press, 2005. Organic *Compounds*; Science (b)http://ibond.nankai.edu.cn.

(9) (a) Liu, W.; Zuo, J.; Li, A.; Bi, C. Chemical Structure-Biological Activity Relationships of α-Substituted Cinnamamides. J. Beij. Med. Coll, 1984, 16, 62-65. (b) Rousée, K.; Bouillon, J.-P.; Couve-Bonnaire, S.; Pannecoucke, X. Stereospecific Synthesis of Tri- and Tetrasubstituted α-Fluoroacrylates by Mizoroki-Heck Reaction. Org. Lett. 2016, 18, 540-543 and references therein. (c) Kaneko, T.; Clark, R.; Ohi, N.; Ozaki, F.; Kawahara, T.; Kamada, A.; Okano, K.; Yokohama, H.; Muramoto, K.; Arai, T.; Ohkuro, M.; Takenaka, O.; Sonoda, J. Preparation of Pyrazinobenzothiazine Derivatives and Analogs for the Treatment of Inflammation and Autoimmune Diseases [P]. WO:9806720, 1998-02-19. (d) Balestra, M.; Mullen, G.; Phillips, E.; Schmiesing, R. Preparation of Novel Quinuclidine Acrylamides for the Treatment or Prophylaxis of Psychotic Disorders and Intellectual Impairment Disorders [P]. WO:200136417, 2001-05-25

(10) (a) Welch, J. T.; Herbert, R. W. The Stereoselective Construction of (Z)-3-Aryl-2-fluoroalkenoates. J. Org. Chem. 1990, 55, 4782-4784. (b) Michida, M.; Mukaiyama, T. A Convenient Method for the Synthesis of (Z)-a-Fluoroacrylates: Lewis Base-Catalyzed Carbonyl Fluoroolefination Using Fluoro(trimethylsilyl)ketene Ethvl Trimethylsilyl Acetal. Chem. Lett. 2008, 37, 890-891. (c) Rousée, K.; Schneider, C.; Couve-Bonnaire, S.; Pannecoucke, X.; Levacher, V.; Hoarau, C. Pd- and Cu-Catalyzed Stereo- and Regiocontrolled Decarboxylative/C-H Fluoroalkenylation of Heteroarenes. Chem. -Eur. J. 2014, 20, 15000-15004. (d) Bouazzaoui, O.; Rousée, K.; Mulengi, J. K.; Bouillon, J.-P.; Couve-Bonnaire, S. Synthesis of a-Fluorinated Acrylates by a Palladium-Catalyzed Decarboxylative Olefination Reaction. Eur. J. Org. Chem. 2018, 3705-3715 and references therein.

(11) (a) Amii, H.; Uneyama, K. C-F Bond Activation in Organic Synthesis. Chem. Rev. 2009, 109, 2119-2183. (b) Shen, O.; Huang, Y.-G.; Liu, C.; Xiao, J.-C.; Chen, Q.-Y.; Guo, Y. Review of Recent Advances in C-F Bond Activation of Aliphatic Fluorides. J. Fluor. Chem. 2015, 179, 14-22. (c) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C-F Bond Activation to Access Fluorinated Building Blocks. Chem. Rev. 2015, 115, 931-972. (d) Chen, W.; Bakewell, C.; Crimmin, M. R. Functionalisation of Carbon-Fluorine Bonds with Main Group Reagents. Synthesis 2017, 49, 810-821. (e) Jaroschik, F. Picking One out of Three: Selective Single C-F Activation in Trifluoromethyl Groups. Chem. - Eur. J. 2018, 24, 14572-14582. (f) Hamel, J.-D.; Paquin, J.-F. Activation of C-F Bonds a to C-C Multiple Bonds. Chem. Commun. 2018, 54, 10224-10239. (g) Fujita, T.: Fuchibe, K.: Ichikawa, J. Transition-Metal-Mediated and -Catalyzed C-F Bond Activation by Fluorine Elimination. Angew. Chem., Int. Ed. 2019, 58, 390-402.

(12) For selected examples of C-F functionalization in polyfluoroarenes, see: (a) Guo, W.-H.; Min, Q.-Q.; Gu, J.-W.; Zhang, X. Rhodium-Catalyzed ortho-Selective C-F Bond Borylation of Polyfluoroarenes with Bpin-Bpin. Angew. Chem., Int. Ed. 2015, 54, 9075-9078. (b) Senaweera, S.; Weaver, J. D. Dual C-F, C-H Functionalization via Photocatalysis: Access to Multifluorinated Biaryls. J. Am. Chem. Soc. 2016, 138, 2520-2523. (c) Kikushima, K.; Grellier, M.; Ohashi, M.; Ogoshi, S. Polyfluoroarenes by Concerted Nucleophilic Aromatic Substitution with a Hydrosilicate. Angew. Chem., Int. Ed. 2017, 56, 16191-16196. (d) Tian, Y.-M.; Guo, X.-N.; Kuntze-Fechner, M. W.; Krummenacher, I.; Braunschweig, H.; Radius, U.; Steffen, A.; Marder, T. B. Selective Photocatalytic C-F Borylation of Polyfluoroarenes by Rh/Ni Dual Catalysis Providing Valuable Fluorinated Arylboronate Esters. J. Am. Chem. Soc. 2018, 140, 17612-17623.

(13) For selected examples of C-F bond functionalization of gemdifluoroalkenes, see: (a) Tian, P.; Feng, C.; Loh, T.-P. Rhodium-Catalysed C(sp²)-C(sp²) Bond Formation via C-H/C-F Activation. Nat. Commun. 2015, 6, 7472-7478. (b) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Monofluoroalkenylation of Dimethylamino Compounds through Radical-Radical Cross-Coupling. Angew. Chem., Int. Ed. 2016, 55, 9416-9421. (c) Thornbury, R. T.; Toste, F. D. Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes. Angew. Chem., Int. Ed. 2016, 55, 11629-11632. (d) Hu, J.; Han, X.; Yuan, Y.; Shi, Z. Stereoselective Synthesis of Z Fluoroalkenes through Copper-Catalyzed Hydrodefluorination of gem-Difluoroalkenes with Water. Angew. Chem., Int. Ed. 2017, 56, 13342-13346. (e) Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of gem-Difluoroalkenes with Unactivated Secondary and Tertiary Alkyl Halides. J. Am. Chem. Soc. 2017, 139, 12632-12637. (f) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. Copper-Catalyzed Regioselective Monodefluoroborylation of Polyfluoroalkenes en Route to Diverse Fluoroalkenes. J. Am. Chem. Soc. 2017, 139, 12855-12862. (g) Kojima, R.; Kubota, K.; Ito, H. Stereodivergent Hydrodefluorination of gem-Difluoroalkenes: Selective Synthesis of (Z)- and (E)-Monofluoroalkenes. Chem. Commun. 2017, 53, 10688-10691. (h) Zhang, J.; Dai, W.; Liu, Q.; Cao, S. Cu-Catalyzed Stereoselective Borylation of gem-Difluoroalkenes with B2pin2. Org. Lett. 2017, 19, 3283-3286. (i) Tan, D.-H.; Lin, E.; Ji, W.-W.; Zeng, Y.-F.; Fan, W.-X.; Li, Q.; Gao, H.; Wang, H. Copper-Catalyzed Stereoselective Defluorinative Borylation and Silylation of gem-Difluoroalkenes. Adv. Synth. Catal. 2018, 360, 1032-1037. (j) Zhou, L.; Zhu, C.; Bi, P.; Feng, C. Ni-Catalyzed Migratory Fluoroalkenylation of Unactivated Alkyl Bromides with gem-Difluoroalkenes. Chem. Sci. 2019, 10, 1144-1149 (14) For selected examples of C-F bond functionalization of α trifluoromethyl alkenes, see: (a) Fuchibe, K.; Hatta, H.; Oh, K.; Oki, R.; Ichikawa, J. Lewis Acid Promoted Single C-F Bond Activation of the CF3 Group: SN1'-Type 3,3-Difluoroallylation of Arenes with 2-Trifluoromethyl-1-alkenes. Angew. Chem., Int. Ed. 2017, 56, 5890-5893. (b) Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. Photoredox Generation of Carbon-Centered Radicals Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics. Angew. Chem., Int. Ed. 2017, 56, 15073-15077. (c) Tian, H.; Yoshizawa, K.; Shiota, Y.; Shimakoshi, H.; Hisaeda, Y.; Imamura, K. Photocatalytic Alkene Reduction by a B₁₂-TiO₂ Hybrid Catalyst Coupled with C-F Bond Cleavage for gem-Difluoroolefin Synthesis. Chem. Commun. 2017, 53, 9478-9481. (d) Li, L.; Xiao, T.; Chen, H.; Zhou, L. Visible-Light-Mediated Two-Fold Unsymmetrical C(sp3)-H Functionalization and Double C-F Substitution. Chem. - Eur. J. 2017, 23, 2249-2254. (e) Liu, Y.; Zhou, Y.; Zhao, Y.; Qu, J. Synthesis of gem-Difluoroallylboronates via FeCl2 - Catalyzed Boration/β-Fluorine Elimination of Trifluoromethyl Alkenes. Org. Lett. 2017, 19, 946-949. (f) Lan, Y.; Yang, F.; Wang, C. Synthesis of gem-Difluoroalkenes via Nickel-Catalyzed Allylic Defluorinative Reductive Cross-Coupling.

- 43 ACS Catal. 2018, 8, 9245-9251. (g) Wu, L.-H.; Cheng, J.-K.; Shen, 44 L.; Shen, Z.-L.; Loh, T.-P. Visible Light-Mediated 45 Trifluoromethylation of Fluorinated Alkenes via C-F Bond Cleavage. Adv. Synth. Catal. 2018, 360, 3894-3899. (h) Lu, X.; Wang, X.-X.; 46 Gong, T.-J.; Pi, J.-J.; He, S.-J.; Fu, Y. Nickel-Catalyzed Allylic 47 Defluorinative Alkylation of Trifluoromethyl Alkenes with Reductive 48 Decarboxylation of Redox-active Esters. Chem. Sci. 2019, 10, 809-49 814. (i) Lin, Z.; Lan, Y.; Wang, C. Synthesis of gem-Difluoroalkenes via Nickel-Catalyzed Reductive C-F and C-O Bond Cleavage. ACS 50 Catal. 2019, 9, 775-780. 51
- (15) The only example for *ipso*-functionalization of a C–F bond in α-trifluoromethyl alkenes, see: Zeng, H.; Zhu, C.; Jiang, H. Single C(sp³) –F Bond Activation in a CF₃ Group: *Ipso*-Defluorooxylation of (Trifluoromethyl)alkenes with Oximes. *Org. Lett.* 2019, *21*, 1130–1133.

(16) (a) O'Hagan, D. Understanding Organofluorine Chemistry. An Introduction to the C–F Bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (b) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591.

(17) The *ipso*-hydrodefluorination of one C–F bond in α -trifluoromethyl alkenes gave the major by-product. For β -CF₃ styrene substrate, it could also underwent a highly selective *ipso*-carboxylation of one C–F bond to give the α,α -difluorocarboxylate, albeit with a much lower efficiency (<20% yield) under our both reaction conditions.

(18) McAlpine, I.; Tran-Dubé, M.; Wang, F.; Scales, S.; Matthews, J.; Collins, M. R.; Nair, S. K.; Nguyen, M.; Bian, J.; Alsina, L. M.; Sun, J.; Zhong, J.; Warmus, J. S.; O'Neill, B. T. Synthesis of Small 3-Fluoro- and 3,3-Difluoropyrrolidines Using Azomethine Ylide Chemistry. *J. Org. Chem.* **2015**, *80*, 7266–7274.

(19) (a) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. Copper(I)-Catalyzed Carboxylation of Aryl- and Alkenylboronic Esters. *Org. Lett.* **2008**, *10*, 2697–2700. (b) Ohmiya, H.; Tanabe, M.; Sawamura, M. Copper-Catalyzed Carboxylation of Alkylboranes with Carbon Dioxide: Formal Reductive Carboxylation of Terminal Alkenes. *Org. Lett.* **2011**, *13*, 1086–1088. (c) Ohishi, T.; Zhang, L.; Nishiura, M.; Hou, Z. Carboxylation of Alkylboranes by N-Heterocyclic Carbene Copper Catalysts: Synthesis of Carboxylic Acids from Terminal Alkenes and Carbon Dioxide. *Angew. Chem. Int. Ed.* **2011**, *50*, 8114– 8117. (d) Juhl, M.; Laursen, S. L. R.; Huang, Y.; Nielsen, D. U.; Daasbjerg, K.; Skrydstrup, T. Copper-Catalyzed Carboxylation of Hydroborated Disubstituted Alkenes and Terminal Alkynes with Cesium Fluoride. *ACS Catal.* **2017**, *7*, 1392–1396.

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