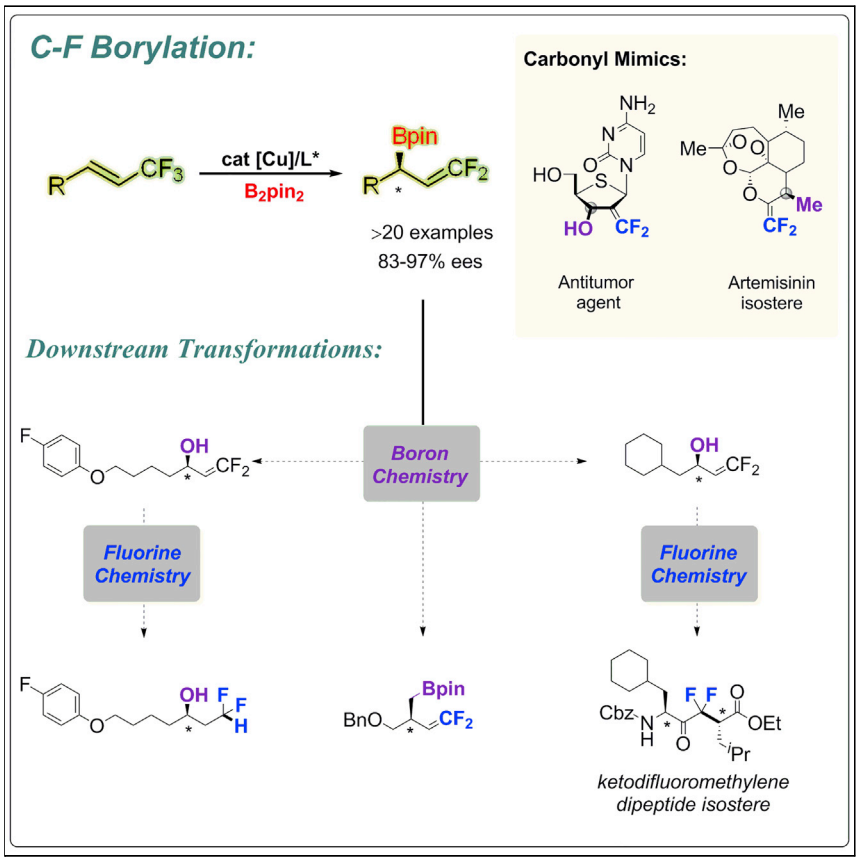
Chem

CellPress

Article

Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes



A mild catalytic system has been established for the asymmetric defluoroborylation of 1-(trifluoromethyl)alkenes via C-F activation. This route employs a low-cost copper catalyst and can be used to generate chiral *gem*-difluoroallylboronates with a broad substrate scope.

Pan Gao, Chengkai Yuan, Yue Zhao, Zhuangzhi Shi

shiz@nju.edu.cn

HIGHLIGHTS

The first asymmetric defluoroborylation

Rapid access to optically active *gem*-difluoroallylboronates

Cheap copper catalysis under mild reaction conditions

Useful carbonyl mimic products based on the diversity of boron chemistry

Gao et al., Chem *4*, 1–11
September 13, 2018
https://doi.org/10.1016/j.chempr.2018.07.003

Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003

Chem

CellPress

Article

Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes

Pan Gao,[1] Chengkai Yuan,[1] Yue Zhao,[1] and Zhuangzhi Shi[1,2,*]

SUMMARY

***gem*-Difluoroalkenes have steric and electronic profiles similar to those of ketones, aldehydes, and esters, and consequently have been used widely as carbonyl isosteres in modern drug discovery. Although many attempts have been made to achieve *gem*-difluoroalkenes, the induction of enantioselectivity at the α position of a *gem*-difluorovinyl group still remains a challenge. Herein, an efficient method for the construction of *gem*-difluoroallylboronates with high enantiomeric excess via a copper-catalyzed defluoroborylation of 1-(trifluoromethyl)alkenes with B_2pin_2 is described. The reaction conditions were mild, and a variety of common functional groups, such as ether, fluoride, chloride, bromide, iodide, ester, cyano, sulfide, amino, and indoyl groups, were well tolerated. Furthermore, we not only applied this developed system as a powerful synthetic tool for the late-stage modification of complex compounds but also highlighted the utility of the formed compounds in synthesis.**

INTRODUCTION

gem-Difluorovinyl groups, important structural motifs in medicinal design, exhibit steric and electronic profiles similar to those of the corresponding carbonyl substituents, and consequently have been used widely as carbonyl isosteres.[1] *gem*-Difluoroalkene mimics of bioactive ketones and esters have been prepared to improve pharmaceutical properties such as bioactivity, target specificity, and metabolic stability of the mimics over those of their bioactive parent structures (Figure 1A).[2–6] Although impressive progress has been made in the synthesis of *gem*-difluoroalkenes in recent years, for example, the classical Wittig olefination and Julia-Kocienski reaction, some issues remain unresolved.[7–18] First, most traditional approaches require strong bases, which leads to a limited substrate scope and low efficiency; second, the α position of a *gem*-difluorovinyl group in a drug candidate is usually a chiral carbon center, and the induction of enantioselectivity at this position is still challenging[19]; third, the rapid and efficient installation of a range of functional groups such as hydroxyl, amino, and alkyl substituents to α position of a difluorovinyl group is in high demand. On the other hand, α-chiral boronate-substituted compounds are an important family of target molecules, because the C-B linkage provides an extremely useful stereogenic center.[20–29] They have been shown to participate in C-C coupling reactions with excellent enantioselectivity.[30,31] Furthermore, the formed chiral C-B bond may be readily converted into a C-O, C-N, and other C-heteroatom bond with retention of the configuration, allowing access to a wide array of functional groups that are common in valuable synthetic targets.[32] Therefore, to address the aforementioned challenges, an efficient method is to construct α-chiral boronate-substituted *gem*-difluoroalkene building blocks.

Defluorinative functionalization of fluorine-containing compounds has shown promise as it confers synthetic versatility to inert C-F bonds.[33–40] Defluoroborylations of

The Bigger Picture

Modern drug discovery relies on advance in chemical synthesis to address challenges from designing new pharmaceutical agents. Replacement of a carbonyl with the corresponding *gem*-difluoroalkene, a carbonyl isostere, has been demonstrated to provide bioactive substrates still recognized by their target. However, this potentially valuable carbonyl mimic has not been more extensively evaluated, possibly because the conventional routes to construct the *gem*-difluoroethylene motif involve a functional-group interconversion relying on highly reactive intermediates, organometallic reagents, or harsh reaction conditions. Our methodology enables C-F activation of 1-(trifluoromethyl)alkenes via a defluoroborylation process to produce a diverse array of enantioenriched *gem*-difluoroallylboronates. We anticipate that the strategy based on the diversity of boron chemistry will simplify the synthesis and structural elaboration of *gem*-difluoroalkene targets in chemistry, biology, and medicine.

Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003

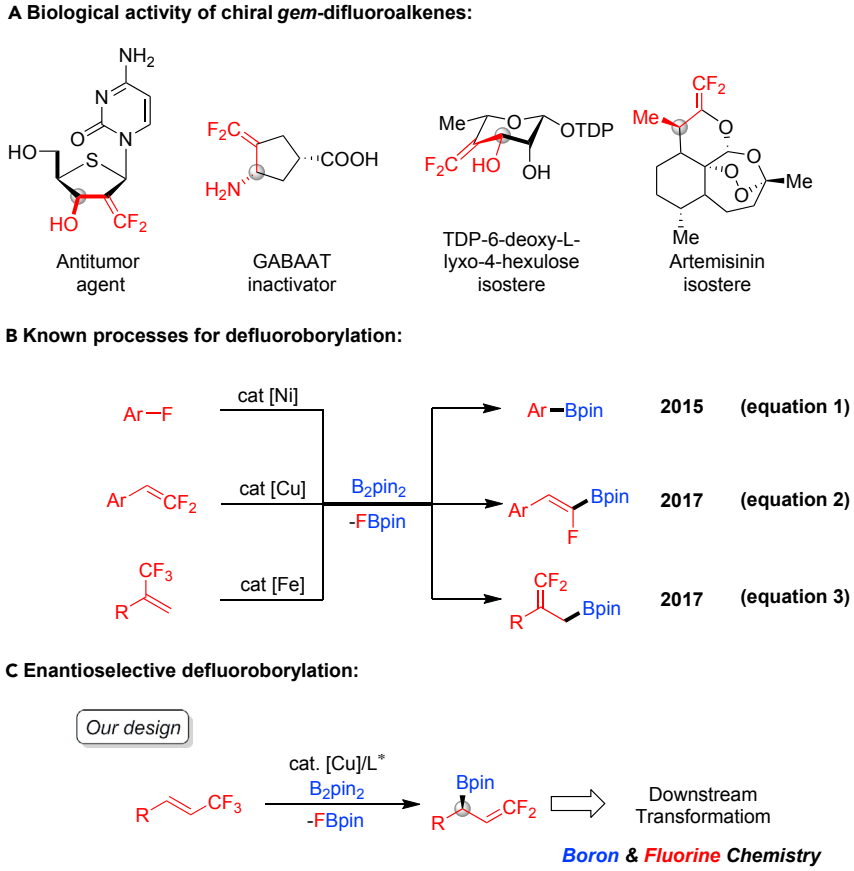


Figure 1. Development of a Protocol to Build Chiral *gem*-Difluoroallylboronates

unactivated fluoroarenes have been reported by several groups (Figure 1B, equation 1).[41–44] Recent progress has been made for the construction of Z-fluoro-alkenylboronates by a Cu-catalyzed stereoselective monodefluoroborylation of *gem*-difluoroalkenes (Figure 1B, equation 2).[45,46] Our group[47] and Ito's group[48] have also developed Cu-catalyzed stereoselective hydrodefluorinations of *gem*-difluoroalkenes to generate Z-fluoroalkenes, in which the Z-fluoro-alkenylboronates acted as the key intermediates. Notably, Fe-catalyzed syntheses of *gem*-difluoroallylboronates via the defluoroborylation of α-(trifluoromethyl)alkenes in the absence of ligand have also been developed (Figure 1B, equation 3).[49] Inspired by these results, here we report a mild and operationally simple strategy for the construction of α-chiral boronate-substituted *gem*-difluoroalkenes through a copper-catalyzed, enantioselective defluoroalkylation of 1-(trifluoromethyl)alkenes (Figures S35–S85) with B_2Pin_2 (Figure 1C). The challenge of this strategy was to cleave a stable C-F bond in a CF_3 group while simultaneously forming a readily transformable allylic C-B bond as part of a stereogenic center.

RESULTS AND DISCUSSION

Initial studies of the catalytic reaction conditions identified Cu salts in conjunction with an N-heterocyclic carbene (NHC) ligand as effective promoters of the addition of B_2pin_2 to 1-(trifluoromethyl)alkene **1a** (Table 1; see also Figures S35–S37). In the presence of 10 mol % CuCl, 11 mol % ICy·HCl, 1.0 equiv NaO^{t}Bu, and 2.0 equiv MeOH at 45°C under an argon atmosphere in CH_3CN, we indeed observed the

[1]State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China

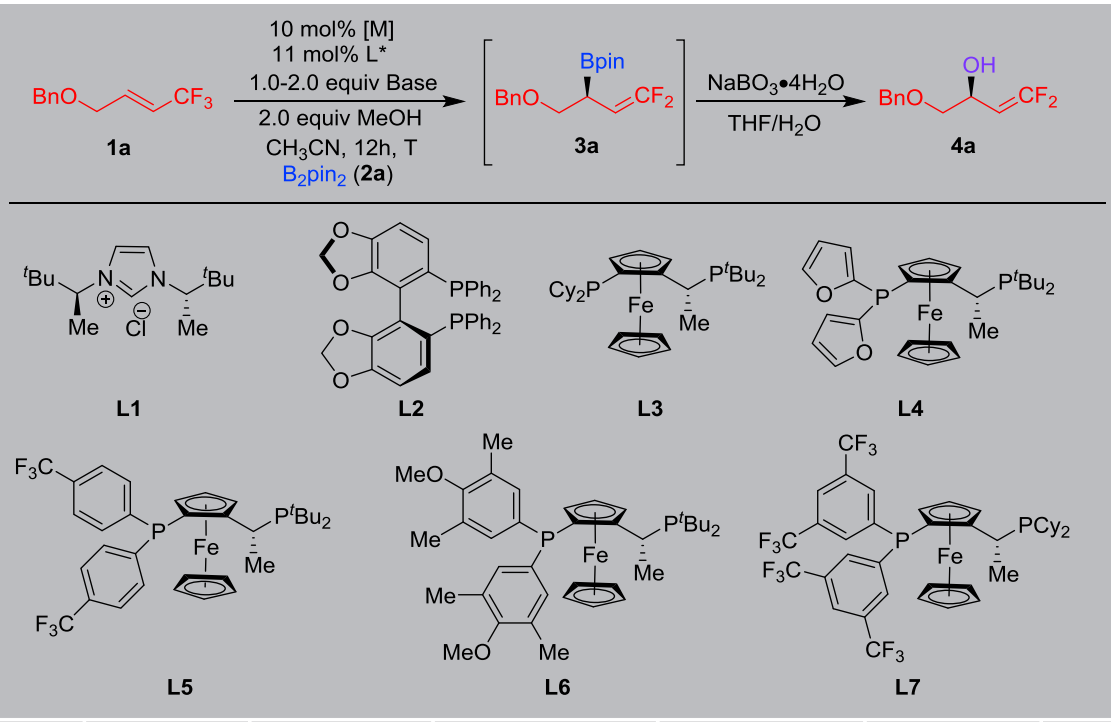
[2]Lead Contact

*Correspondence: shiz@nju.edu.cn

https://doi.org/10.1016/j.chempr.2018.07.003

Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003

Table 1. Reaction Development

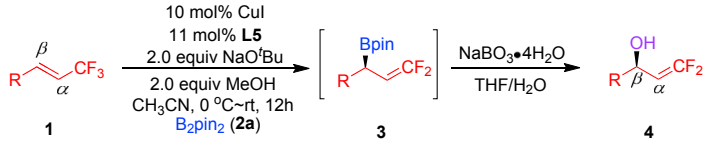


Entry	[M]	L*	Base (equiv)	Temp. (°C)	ee (%)[a]	Yield of 4a (%)[b]
1	CuCl	ICy·HCl	NaO^{t}Bu (1.0)	45	–	18
2	CuI	ICy·HCl	NaO^{t}Bu (1.0)	45	–	32
3	CuI	ICy·HCl	NaO^{t}Bu (2.0)	45	–	84 (58)[c]
4	CuI	L1	NaO^{t}Bu (2.0)	45	5	89
5	CuI	L2	NaO^{t}Bu (2.0)	45	21	90
6	CuI	L3	NaO^{t}Bu (2.0)	45	54	83
7	CuI	L4	NaO^{t}Bu (2.0)	45	82	88
8	CuI	L5	NaO^{t}Bu (2.0)	45	88	90
9	CuI	L6	NaO^{t}Bu (2.0)	45	75	76
10	CuI	L7	NaO^{t}Bu (2.0)	45	84	85
11	CuI	L5	NaO^{t}Bu (2.0)	RT	89	91
12	CuI	L5	NaO^{t}Bu (2.0)	0	92	68
13	**CuI**	**L5**	**NaO^{t}Bu (2.0)**	**0–RT**	**92**	**89 (65)[c]**
14[d]	CuI	L5	NaO^{t}Bu (2.0)	0–RT	–	trace
15[e]	CuI	L5	–	0–RT	–	trace
16	FeCl2	L5	NaO^{t}Bu (2.0)	0–RT	–	0

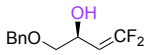
Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol) in CH_3CN (2.0 mL), 12 hr, room temperature (RT), under Ar.
[a]Enantiomeric excess values were determined by chiral high-performance liquid chromatography analysis.
[b]Isolated yield after chromatography.
[c]Isolated yield of **3a**.
[d]Without MeOH.
[e]Without NaO^{t}Bu.

formation of defluoroborylation product **3a** and isolated the corresponding alcohol product **4a** in 18% yield after Brown oxidation by $NaBO_3$ (entry 1). Other copper salts such as CuI showed better yields (entry 2). The use of 2.0 equiv of NaO^{t}Bu resulted in

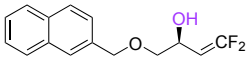
Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003



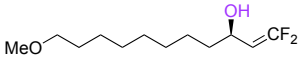
1 3 4



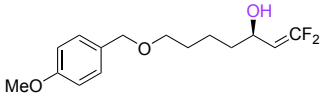
4a
89%, 92% ee



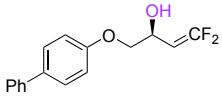
4b
78%, 94% ee



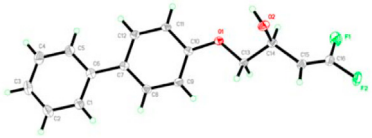
4c
82%, 85% ee



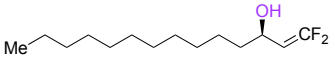
4d
83%, 91% ee



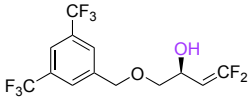
4e
59%, 93% ee



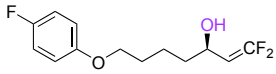
CCDC 1821460



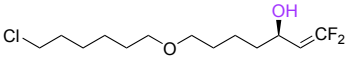
4f
67%, 88% ee



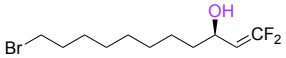
4g
92%, 93% ee



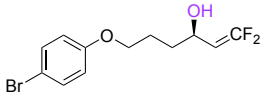
4h
88%, 95% ee



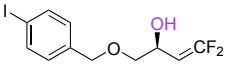
4i
76%, 91% ee



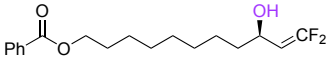
4j
87%, 90% ee



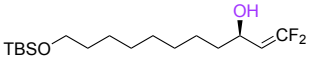
4k
83%, 85% ee



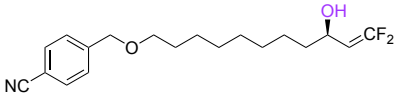
4l
76%, 90% ee



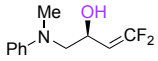
4m
50%, 92% ee



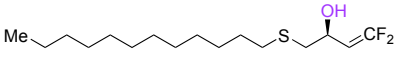
4n
63%, 83% ee



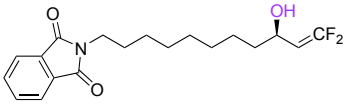
4o
72%, 87% ee



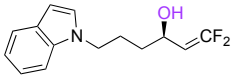
4p
82%, 90% ee



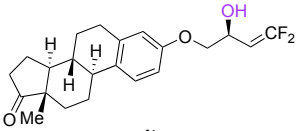
4q
58%, 93% ee



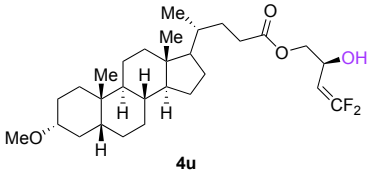
4r
64%, 90% ee



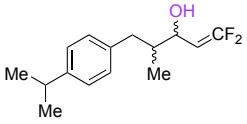
4s
82%, 89% ee



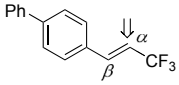
4t
62%, 86% de



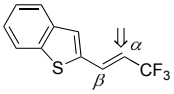
4u
44%, 99% de



4v
32%, dr = 3: 2



1w



1x

Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003

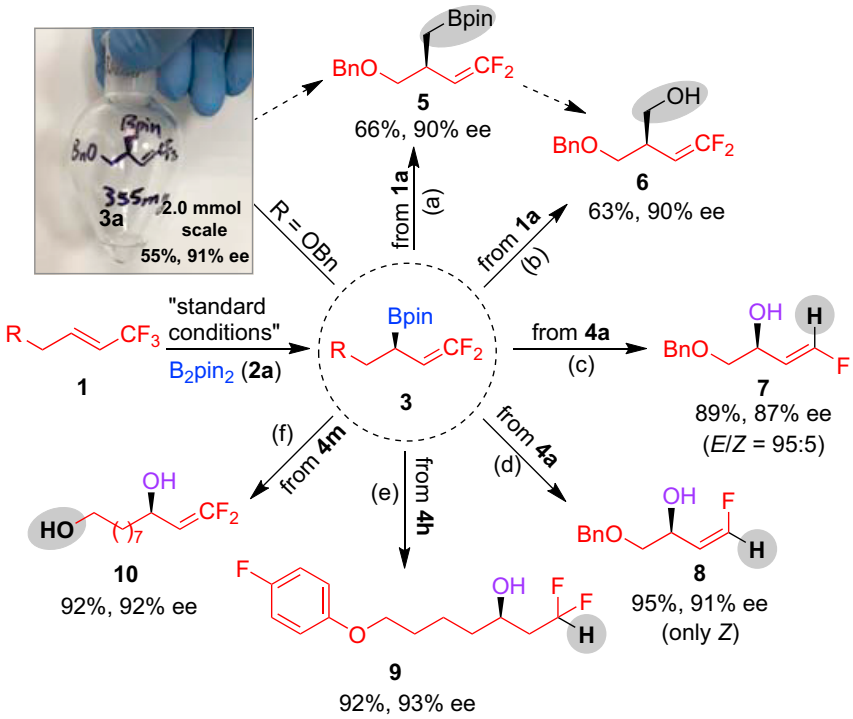
Figure 2. Substrate Scope

Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), CuI (10 mol % mmol), **L5** (11 mol % mmol), NaO^{t}Bu (0.40 mmol), B_2pin_2 (0.4 mmol), MeOH (0.40 mmol) in CH_3CN (2.0 mL), 12 hr, 0°C to room temperature (RT), under Ar, isolated yield after chromatography. For **4j** and **4q**, 0°C, 12 hr. For **4v**, diastereoselectivity was determined by high-performance liquid chromatography analysis.

84% isolated yield of **4a**, despite precursor **3a** being unstable on silica gel column (only 58% isolated yield, entry 3). To achieve an enantioselective variation, we first evaluated chiral NHC ligands such as **L1**, which only afforded 5% enantiomeric excess (ee) (entry 4). We found bidentate phosphine ligands such as (S)-SEGPHOS (entry 5) to be more effective, and we discovered that the JOSIPHOS family of ligands provided the best reactivity and enantioselectivity (entries 6–10). Among them, the use of the (R, S_p)-**L5**, bearing P(4-CF_3Ph)$_2$ and P^{t}Bu$_2$ substituents, provided the desired product **4a** in 90% yield and 88% ee (entry 8). With the more active catalyst system, it was found that reactions of **1a** could be conducted at room temperature (RT) (entry 11) and even 0°C (entry 12), leading to a slight increase in enantioselectivity. The greatest enhancement in reactivity (88%, 92% ee) was observed when the reaction was slowly warmed from 0°C to RT (entry 13; see also Figures S8 and S89–S91). Control experiments revealed that the absence of MeOH or NaO^{t}Bu dramatically reduced the yield (entries 14 and 15). The choice of copper catalysis was critical, while the reaction could not work in the presence of $FeCl_2$ (entry 16).[49]

With the optimized reaction conditions in hand, we then examined the scope of this defluoroborylation reaction (Figure 2). The naphthyl group of substrate **1b** (Figures S38–S40) did not hinder the defluoroborylation process, and the reaction afforded corresponding product **4b** (Figures S9 and S92–S94) in 78% yield and 94% ee. Asymmetric defluoroborylations of 1-(trifluoromethyl)alkenes with either ester (**4c**; Figures S10 and S95–S97) or anisole (**4d**; Figures S11 and S98–S100) moieties on a distal position proceeded smoothly. Biphenyl-containing substrate **1e** was tolerated and gave product **4e** (Figures S12 and S101–S103) in 93% ee. To determine the absolute configuration of our products, we grew crystals of compound **4e** and subjected them to X-ray crystallographic analysis (Figure 2; see also Figure S6 and Tables S1, S2, S3, S4, and S5). A non-activated linear olefin could be transformed successfully under the reaction conditions as well (**4f**; Figures S13 and S104–S106). Reactions of **1g** (Figures S47–S49) and **1h** (Figures S50–S52), which contain multiple sites for possible C-F borylation, showed extremely high selectivity for C-F activation at the vinyl-fluoro functionality over the alkyl terminal position (**4g-4h**; Figures S14, S15, and S107–S112). It should be noted that the chemoselectivity of the chiral copper catalyst was not affected by halo substituents such as Cl (**4i**; Figures S16 and S113–S115), Br (**4j-4k**; Figures S17, S18, and S116–S121), and I (**4l**; Figures S19, and S122–S124) on the substrates, highlighting the potential of this process in combination with subsequent conventional cross-coupling transformations. Adducts **4m** (Figures S20 and S125–S127) and **4n** (Figures S21 and S128–S130) were formed by the coupling of the corresponding Bz- and TBS-protected alcohols with B_2pin_2, respectively. Substrate **1o** (Figures S71–S73), with a cyano group, was found to be compatible with the reaction conditions and produced product **4o** (Figures S22 and S131–S133) in 72% yield with 87% ee. Notably, substrates with strong coordination abilities, such as those with amine (**4p**; Figures S23 and S134–S136), sulfide (**4q**; Figures S24 and S137–S139) and *O*-phthalimide (**4r**; Figures S25 and S140–S142) moieties, still underwent the defluoroborylation to afford the desired products in good yields. In addition, indole-containing compound **1s** (Figures S80–S82) was also accommodated with minimal impact on yield or enantioselectivity (82% yield, 89% ee; see also Figures S26 and S143–S145). Finally, having established an enantioselective defluoroborylation of

Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003



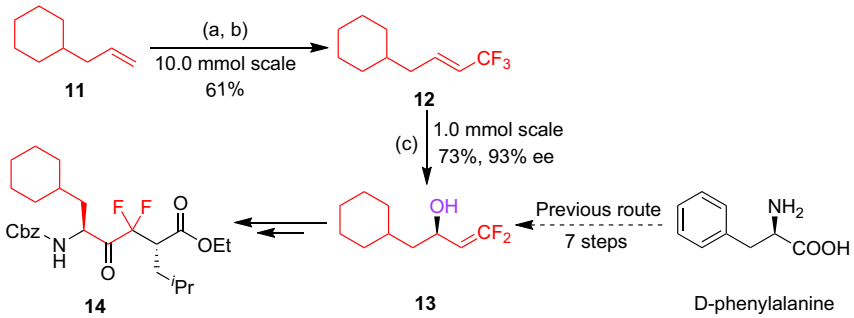
Scheme 1. Enantioenriched *gem*-Difluoroallylboronates as Versatile Intermediates

Reagents and conditions: (a) **1a** (0.20 mmol), **2a** (0.40 mmol), NaO^{t}Bu (0.40 mmol), MeOH (0.40 mmol) in CH_3CN (1.0 mL), 12 hr, 0°C to RT, under Ar; solvent was removed and CH_2ICl (0.50 mmol) and ^{n}BuLi (0.30 mmol) were added in THF (1.0 mL), 12 hr, 0°C; (b) then $NaBO_3 \cdot 4H_2O$ (0.40 mmol), THF/H_2O, 2 hr, RT, under Ar; (c) **4a** (0.20 mmol), red Al (0.24 mmol), toluene, 12 hr, 80°C, under Ar; (d) **4a** (0.20 mmol), CuTc (10 mol % mmol), Xantphos (10 mol % mmol), LiO^{t}Bu (0.60 mmol), B_2pin_2 (0.60 mmol), H_2O (0.60 mmol), DMA (1.0 mL), 16 hr, 40°C, under Ar; (e) **4h** (0.20 mmol), Pd/C (10 mol % mmol), 1 atm H_2, THF (1.0 mL), 6 hr, RT; (f) **4m** (0.20 mmol), NaOH (2.0 mmol), MeOH/H_2O (20:1), 30 min, RT.

1-(trifluoromethyl)alkenes with relatively simple molecules, we applied this strategy to compounds derived from complex natural products. Substrate **1t**, derived from estrone, allowed the diastereoselective construction of product **4t** (Figures S27 and S146–S148) in 62% yield with 86% diastereomeric excess. In addition, lithocholic acid derivative **1u** (Figures S83–S85) was borylated with excellent diastereoselectivity. The reactivity was sensitive to substrate structure, and defluoroborylation of trifluoropropene substrate **1v** containing a secondary alkyl substituent only afforded a mixture of diastereoisomers **4v** (Figures S1 and S152–S154) in low conversion. When β-(hetero)ary-containing 1-(trifluoromethyl)alkenes such as **1w** and **1x** were subjected to the reaction, only a small amount of α-boronate addition products were generated at the current reaction conditions.

To showcase the practical utility of our copper-catalyzed asymmetric defluoroborylation process, we conducted a 2.0-mmol reaction and obtained *gem*-difluoroallylboronate **3a** (Figures S7 and S86–S88) in 55% yield and 92% ee following flash column chromatography on silica gel (Scheme 1). As noted at the outset, enantioenriched products bearing both boronate and *gem*-difluorovinyl groups are extremely versatile intermediates in organic synthesis as they can be converted to other important families of compounds with retention of the ee at the boron-bound carbon. Several illustrative examples are provided. Boronate **5** (Figures S155–S157), with an additional methylene unit, can be generated from substrate

Please cite this article in press as: Gao et al., Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.07.003



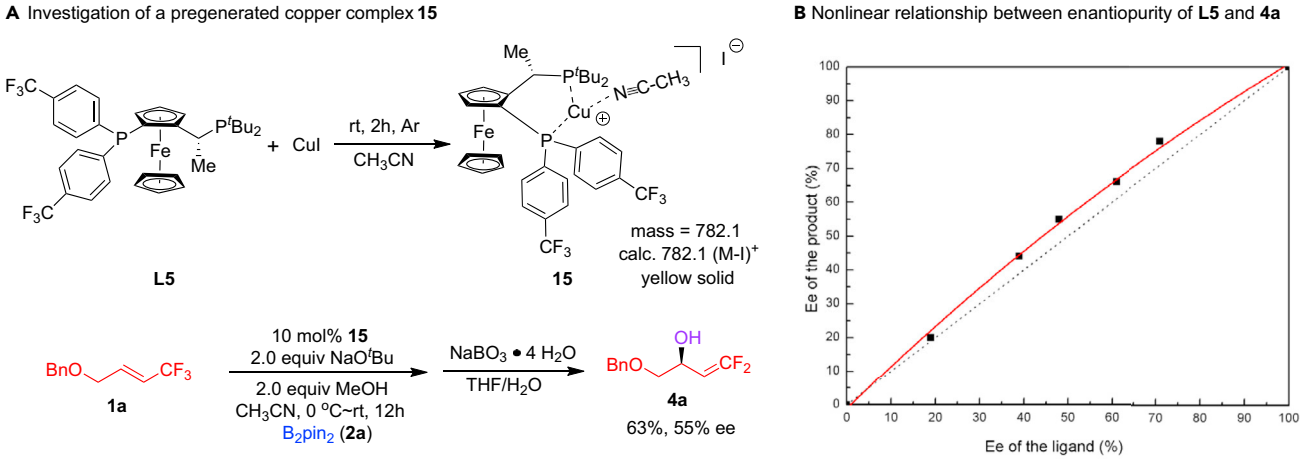
Scheme 2. Application of Our Developed Method as a Key Step in the Synthesis of a Ketodifluoromethylene Dipeptide Isostere

Reagents and conditions: (a) **11** (10.0 mmol), $NaSO_2CF_3$ (30.0 mmol), I_2O_5 (20.0 mmol), DCM/H_2O (4:1), 12 hr, 110°C; (B) DBU (20.0 mmol), DCM, 2 hr, RT; (C) **12** (1.0 mmol), CuI (10 mol %), **L5** (11 mol %), NaO^tBu (2.0 mmol), B_2pin_2 (2.0 mmol), MeOH (2.0 mmol), CH_3CN (10.0 mL), 12 hr, 0°C to RT, under Ar.

1a through a tandem homologation with the *in situ*-formed CH_2ClLi reagent in 66% yield and 90% ee.[50,51] This crude reaction mixture can be used to further generate corresponding homoallylic *gem*-difluoroallyl alcohol **6** (Figures S29 and S158–S160) in 63% yield and 90% ee. Reduction of **4a** with red Al afforded *E*-fluoroalkene **7** (Figures S30 and S161–S163) in 89% yield and 87% ee (*E*/*Z* = 95:5). Alternatively, utilizing our recently developed method for copper-catalyzed hydrodefluorinations of *gem*-difluoroalkenes with water could afford the Z-fluoroalkene **8** (Figures S31 and S164–S166) in 95% yield without loss of ee.[47] The double bond in product **4h** could be hydrogenated to yield CF_2H-substituted alkane **9** (Figures S32 and S167–S169) in 92% yield and 92% ee. In addition, hydrolysis product **4m** afforded access to diol **10** (Figures S33 and S170–S172) without erosion of the enantiopurity.

The utility of our strategy can also be exemplified by its use in a key step in the asymmetric synthesis of ketodifluoromethylene dipeptide isostere **14** (Scheme 2). Our synthesis commenced with the preparation of 1-(trifluoromethyl)alkene **12** (Figures S173–S175) from commercially available olefin **11**. The reaction of **12** with B_2pin_2 (**2a**) under the optimized conditions formed key intermediate **13** (Figures S34 and S176–S178) in 73% yield and 94% ee, which was prepared from D-phenylalanine in seven steps in a previous route.[52] We envisaged that this efficient method could be used for the diversity-oriented synthesis of ketodifluoromethylene dipeptide isosteres for medicinal applications in the future.

How bidentate phosphine ligands induce high levels of enantioselectivity in the transition metal-catalyzed asymmetric reactions has been a topic of interest for some time. Independent generation of the 1:1 CuI:**L5** complex in CH_3CN afforded a yellow solid copper complex **15** (Figures S2–S4) confirmed by electrospray ionization mass spectrometry and ^{31}P- and ^{1}H-nuclear magnetic resonance studies. However, copper complex **15** did not prove to be a competent catalyst in the presence of 1-(trifluoromethyl)alkene **1a** and B_2pin_2 (**2a**), identical to the CuI/**L5** system in terms of yield and enantioselectivity (Scheme 3A). This result indicates that complex **15** is not a true catalyst for our reaction. To provide more insights into the mechanism of the present catalytic system, we examined nonlinear effects (NLE)[53] of the copper-catalyzed asymmetric defluoroborylation of 1-(trifluoromethyl)alkenes using **L5** with varying ee as the ligand under the optimized reaction conditions. A weak



Scheme 3. Mechanistic Experiments

positive NLE was observed (Scheme 3B), indicating that the copper(I) species involved in the catalysis should contain more than one bidentate phosphine ligand within or at the periphery of the catalytic cycle.[54]

From these experimental results and literature precedent, the proposed mechanism of the Cu-catalyzed chiral *gem*-difluoroallylboronate formation is shown in Figure 3. The reaction of the precatalyst (CuI), chiral ligand, and NaO^{t}Bu forms the catalytically active species (**A**). This complex can easily undergo transmetalation with the anionic adduct of B_2pin_2 (**2a′**)[55,56] to generate intermediate **B**. Reaction of 1-(trifluoromethyl)alkenes (**1**, R = alkyl), was found to afford only C-B bonds at the β position. Such preferences were attributed to conjugate CF3 substituent (**C**). While using 1-(trifluoromethyl)alkenes (**1**, R = (hetero)aryl) such as **1w-1x** as substrates, C-Cu bond formation may be electronically favored at the benzylic position stabilization by the (hetero)aryl group (**C′**).[57–62] After further enantioselective formation of intermediate **D**, *cis* β-F elimination[33–40,45–49] delivers the final product **3** and a CuF-like species **E**, which can undergo anion exchange with NaO^{t}Bu to regenerate the copper catalyst.

Conclusion

In summary, we have developed an efficient asymmetric copper-catalyzed system that can activate the C-F bonds of 1-(trifluoromethyl)alkenes via a defluoroborylation process to produce a diverse array of enantioenriched *gem*-difluoroallylboronates.[63] Given the ubiquity of the *gem*-difluorovinyl group and its precursors in bioactive compounds, we anticipate that this strategy based on the diversity of boron chemistry will simplify the synthesis and structural elaboration of *gem*-difluoroalkene targets for research in chemistry, biology, and medicine.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND SOFTWARE AVAILABILITY

The crystallography data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession number CCDC: 1821460 (**4e**) and can be obtained free of charge from www.ccdc.cam.ac.uk/getstructures.

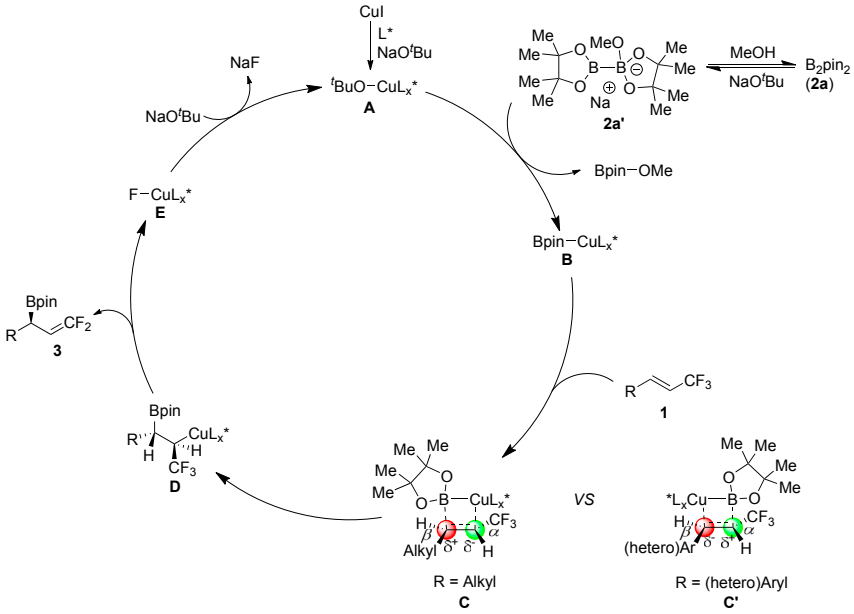


Figure 3. Proposed Catalytic Cycle

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 178 figures, 5 tables, and 1 data file and can be found with this article online at https://doi.org/10.1016/j.chempr.2018.07.003.

ACKNOWLEDGMENTS

We thank the "1000-Youth Talents Plan" and the National Natural Science Foundation of China (Grant 2167020084) for their financial support.

AUTHOR CONTRIBUTIONS

Z.S. conceived and designed the study and wrote the paper. P.G. and C.Y. performed the experiments and mechanism study and analyzed the data. Y.Z. performed the crystallographic studies.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: March 13, 2018
Revised: May 14, 2018
Accepted: July 6, 2018
Published: July 26, 2018

REFERENCES AND NOTES

1. Uneyama, K. (2006). Hydrogen Bonding in Organofluorine Compounds in Organofluorine Chemistry (Blackwell Publishing), pp. 173–185.

2. Lim, M.H., Kim, H.O., Moon, H.R., Chun, M.W., and Jeong, L.S. (2002). Synthesis of novel D-2′-deoxy-2′-*C*-difluoromethylene-4′-thiocytidine as a potential antitumor agent. Org. Lett. *4*, 529–531.

3. Leriche, C., He, X., Chang, C.-W., and Liu, H.-W. (2003). Reversal of the apparent regiospecificity of NAD(P)H-dependent hydride transfer: the properties of the difluoromethylene group, a carbonyl mimic. J. Am. Chem. Soc. *125*, 6348–6349.

4. Pan, Y., Qiu, J., and Silverman, R.B. (2003). Design, synthesis, and biological activity of a difluoro-substituted, conformationally rigid vigabatrin analogue as a potent γ-aminobutyric acid aminotransferase inhibitor. J. Med. Chem. *46*, 5292–5293.

5. Altenburger, J.M., Lassalle, G.Y., Matrougui, M., Galtier, D., Jetha, J.C., Bocskei, Z., Berry, C.N., Lunven, C., Lorrain, J., Herault, J.P., et al. (2004). SSR182289A, a selective and potent

orally active thrombin inhibitor. Bioorg. Med. Chem. *12*, 1713–1730.

6. Magueur, G., Crousse, B., Ourévitch, M., Bonnet-Delpon, D., and Bégué, J.P. (2006). Fluoro-artemisinins: when a *gem*-difluoroethylene replaces a carbonyl group. J. Fluor. Chem. *127*, 637–642.

7. Chelucci, G. (2012). Synthesis and metal-catalyzed reactions of *gem*-dihalovinyl systems. Chem. Rev. *112*, 1344–1462.

8. Liu, Y., Deng, M., Zhang, Z., Ding, X., Dai, Z., and Guan, J. (2012). Progress in preparation of *β,β*-difluorovinyl compounds. Youji Huaxue *32*, 661–666.

9. Prakash, G.K.S., Hu, J., Wang, Y., and Olah, G.A. (2004). Difluoromethyl phenyl sulfone, a difluoromethylidene equivalent: use in the synthesis of 1,1-difluoro-1-alkenes. Angew. Chem. Int. Ed. *43*, 5203–5206.

10. Miura, T., Ito, Y., and Murakami, M. (2008). Synthesis of *gem*-difluoroalkenes via β-fluoride elimination of organorhodium(I). Chem. Lett. *37*, 1006–1007.

11. Zhao, Y., Huang, W., Zhu, L., and Hu, J. (2010). Difluoromethyl 2-pyridyl sulfone: a new *gem*-difluoroolefination reagent for aldehydes and ketones. Org. Lett. *12*, 1444–1447.

12. Zheng, J., Cai, J., Lin, J.-H., Guo, Y., and Xiao, J.-C. (2013). Synthesis and decarboxylative wittig reaction of difluoromethylene phosphobetaine. Chem. Commun. *49*, 7513–7515.

13. Hu, M., He, Z., Gao, B., Li, L., Ni, C., and Hu, J. (2013). Copper-catalyzed *gem*-difluoroolefination of diazo compounds with $TMSCF_3$ via C-F bond cleavage. J. Am. Chem. Soc. *135*, 17302–17305.

14. Gao, B., Zhao, Y., Hu, M., Ni, C., and Hu, J. (2014). *gem*-Difluoroolefination of diaryl ketones and enolizable aldehydes with difluoromethyl 2-pyridyl sulfone: new insights into the Julia-Kocienski reaction. Chem. Eur. J. *20*, 7803–7810.

15. Hu, M., Ni, C., Li, L., Han, Y., and Hu, J. (2015). *gem*-Difluoroolefination of diazo compounds with $TMSCF_3$ or $TMSCF_2Br$: transition-metal-free cross-coupling of two carbene precursors. J. Am. Chem. Soc. *137*, 14496–14501.

16. Gao, B., Zhao, Y., Hu, J., and Hu, J. (2015). Difluoromethyl 2-pyridyl sulfone: a versatile carbonyl *gem*-difluoroolefination reagent. Org. Chem. Front. *2*, 163–168.

17. Zhang, Z., Yu, W., Wu, C., Wang, C., Zhang, Y., and Wang, J. (2017). Reaction of diazo compounds with difluorocarbene: an efficient approach towards 1,1-difluoroolefins. Angew. Chem. Int. Ed. *55*, 273–277.

18. Fuchibe, K., Hatta, H., Oh, K., Oki, R., and Ichikawa, J. (2017). Lewis acid promoted single C-F bond activation of the CF_3 group: S_N1'-type 3,3-difluoroallylation of arenes with 2-trifluoromethyl-1-alkenes. Angew. Chem. Int. Ed. *56*, 5890–5893.

19. Huang, Y., and Hayashi, T. (2016). Rhodium-catalyzed asymmetric arylation/defluorination of 1-(trifluoromethyl)alkenes forming enantioenriched 1,1-difluoroalkenes. J. Am. Chem. Soc. *138*, 12340–12343.

20. Collins, B.S.L., Wilson, C.M., Myers, E.L., and Aggarwal, V.K. (2017). Asymmetric synthesis of secondary and tertiary boronic esters. Angew. Chem. Int. Ed. *56*, 11700–11733.

21. Neeve, E.C., Geier, S.J., Mkhalid, I.A.I., Westcott, S.A., and Marder, T.B. (2016). Diboron(4) compounds: from structural curiosity to synthetic workhorse. Chem. Rev. *116*, 9091–9161.

22. Xu, L., Zhang, S., and Li, P. (2015). Boron-selective reactions as powerful tools for modular synthesis of diverse complex molecules. Chem. Soc. Rev. *44*, 8848–8858.

23. Mlynarski, S.N., Schuster, C.H., and Morken, J.P. (2014). Asymmetric synthesis from terminal alkenes by cascades of diboration and cross-coupling. Nature *505*, 386–390.

24. Zhang, L., Lovinger, G.J., Edelstein, E.K., Szymaniak, A.A., Chierchia, M.P., and Morken, J.P. (2016). Catalytic conjunctive cross-coupling enabled by metal-induced metallate rearrangement. Science *351*, 70–74.

25. Schmidt, J., Choi, J., Liu, A.T., Slusarczyk, M., and Fu, G.C. (2016). A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters. Science *354*, 1265–1269.

26. He, J., Shao, Q., Wu, Q., and Yu, J.-Q. (2017). Pd(II)-catalyzed enantioselective $C(sp^3)$-H borylation. J. Am. Chem. Soc. *139*, 3344–3347.

27. Smith, J.R., Collins, B.S.L., Hesse, M.J., Graham, M.A., Myers, E.L., and Aggarwal, V.K. (2017). Enantioselective rhodium(III)-catalyzed markovnikov hydroboration of unactivated terminal alkenes. J. Am. Chem. Soc. *139*, 9148–9151.

28. Lee, J., Torker, S., and Hoveyda, A.H. (2017). Versatile homoallylic boronates by chemo-, S_N2'-, diastereo- and enantioselective catalytic sequence of Cu-H addition to vinyl-B(pin)/allylic substitution. Angew. Chem. Int. Ed. *56*, 821–826.

29. Cai, Y., Yang, X.-T., Zhang, S.-Q., Li, F., Li, Y.-Q., Ruan, L.-X., Hong, X., and Shi, S.-L. (2018). Copper-catalyzed enantioselective markovnikov protoboration of α-olefins enabled by a buttressed N-heterocyclic carbene ligand. Angew. Chem. Int. Ed. *57*, 1376–1380.

30. Bigler, R., and Aggarwal, V.K. (2018). *ortho*-Directing chromium arene complexes as efficient mediators for enantiospecific $C(sp^2)$-$C(sp^3)$ cross-coupling reactions. Angew. Chem. Int. Ed. *57*, 1082–1086.

31. Wilson, C.M., Ganesh, V., Noble, A., and Aggarwal, V.K. (2017). Enantiospecific sp^2-sp^3 coupling of *ortho*- and *para*-phenols with secondary and tertiary boronic esters. Angew. Chem. Int. Ed. *56*, 16318–16322.

32. Sandford, C., and Aggarwal, V.K. (2017). Stereospecific functionalizations and transformations of secondary and tertiary boronic esters. Chem. Commun. *53*, 5481–5494.

33. Amii, H., and Uneyama, K. (2009). C-F bond activation in organic synthesis. Chem. Rev. *109*, 2119–2183.

34. Ahrens, T., Kohlmann, J., Ahrens, M., and Braun, T. (2015). Functionalization of fluorinated molecules by transition-metal-mediated C-F bond activation to access fluorinated building blocks. Chem. Rev. *115*, 931–972.

35. Fuchibe, K., Mayumi, Y., Zhao, N., Watanabe, S., Yokota, M., and Ichikawa, J. (2013). Domino synthesis of fluorine-substituted polycyclic aromatic hydrocarbons: 1,1-difluoroallenes as synthetic platforms. Angew. Chem. Int. Ed. *52*, 7825–7828.

36. Gao, B., Zhao, Y., and Hu, J. (2015). AgF-mediated fluorinative cross-coupling of two olefins: facile access to α-CF_3 alkenes and β-CF_3 ketones. Angew. Chem. Int. Ed. *54*, 638–642.

37. Xie, J., Yu, J., Rudolph, M., Rominger, F., and Hashmi, A.S.K. (2016). Monofluoroalkenylation of dimethylamino compounds through radical-radical cross-coupling. Angew. Chem. Int. Ed. *55*, 9416–9421.

38. Thornbury, R.T., and Toste, F.D. (2016). Palladium-catalyzed defluorinative coupling of 1-aryl-2,2-difluoroalkenes and boronic acids: stereoselective synthesis of monofluorostilbenes. Angew. Chem. Int. Ed. *55*, 11629–11632.

39. Wu, J.-Q., Zhang, S.-S., Gao, H., Qi, Z., Zhou, C.-J., Ji, W.-W., Liu, Y., Chen, Y., Li, Q., Li, X., and Wang, H. (2017). Experimental and theoretical studies on rhodium-catalyzed coupling of benzamides with 2,2-difluorovinyl tosylate: diverse synthesis of fluorinated heterocycles. J. Am. Chem. Soc. *139*, 3537–3545.

40. Sakaguchi, H., Ohashi, M., and Ogoshi, S. (2018). Fluorinated vinylsilanes from the copper-catalyzed defluorosilylation of fluoroalkene feedstocks. Angew. Chem. Int. Ed. *57*, 328–332.

41. Liu, X.-W., Echavarren, J., Zarate, C., and Martin, R. (2015). Ni-catalyzed borylation of aryl fluorides via C-F cleavage. J. Am. Chem. Soc. *137*, 12470–12473.

42. Niwa, T., Ochiai, H., Watanabe, Y., and Hosoya, T. (2015). Ni/Cu-catalyzed defluoroborylation of fluoroarenes for diverse C-F bond functionalizations. J. Am. Chem. Soc. *137*, 14313–14318.

43. Zhou, J., Kuntze-Fechner, M.W., Bertermann, R., Paul, U.S.D., Berthel, J.H.J., Friedrich, A., Du, Z., Marder, T.B., and Radius, U. (2016). Preparing (multi)fluoroarenes as building blocks for synthesis: nickel-catalyzed borylation of polyfluoroarenes via C-F bond cleavage. J. Am. Chem. Soc. *138*, 5250–5253.

44. Niwa, T., Ochiai, H., and Hosoya, T. (2017). Copper-catalyzed *ipso*-borylation of fluoroarenes. ACS Catal. *7*, 4535–4541.

45. Zhang, J., Dai, W., Liu, Q., and Cao, S. (2017). Cu-catalyzed stereoselective borylation of *gem*-difluoroalkenes with B_2pin_2. Org. Lett. *19*, 3283–3286.

46. Sakaguchi, H., Uetake, Y., Ohashi, M., Niwa, T., Ogoshi, S., and Hosoya, T. (2017). Copper-catalyzed regioselective monodefluoroborylation of polyfluoroalkenes en route to diverse fluoroalkenes. J. Am. Chem. Soc. *139*, 12855–12862.

47. Hu, J., Han, X., Yuan, Y., and Shi, Z. (2017). Stereoselective synthesis of *Z* fluoroalkenes through copper-catalyzed hydrodefluorination of *gem*-difluoroalkenes with water. Angew. Chem. Int. Ed. *56*, 13342–13346.

48. Kojima, R., Kubota, K., and Ito, H. (2017). Stereodivergent hydrodefluorination of *gem*-difluoroalkenes: selective synthesis of (*Z*)- and (*E*)-monofluoroalkenes. Chem. Commun. *53*, 10688–10691.

49. Liu, Y., Zhou, Y., Zhao, Y., and Qu, J. (2017). Synthesis of *gem*-difluoroallylboronates via $FeCl_2$-catalyzed boration/β-fluorine elimination of trifluoromethyl alkenes. Org. Lett. *19*, 946–949.

50. Sadhu, K.M., and Matteson, D.S. (1985). (Chloromethyl)lithium: efficient generation and capture by boronic esters and a simple preparation of diisopropyl (chloromethyl) boronate. Organometallics *4*, 1687–1689.

51. Sonawane, R.P., Jheengut, V., Rabalakos, C., Larouche-Gauthier, R., Scott, H.K., and Aggarwal, V.K. (2011). Enantioselective construction of quaternary stereogenic centers from tertiary boronic esters: methodology and applications. Angew. Chem. Int. Ed. *50*, 3760–3763.

52. Damon, D.B., and Hoover, D.J. (1990). Synthesis of the ketodifluoromethylene dipeptide isostere. J. Am. Chem. Soc. *112*, 6439–6442.

53. Girard, C., and Kagan, H.B. (1998). Nonlinear effects in asymmetric synthesis and stereoselective reactions: ten years of investigation. Angew. Chem. Int. Ed. *37*, 2922–2959.

54. Dong, K., Wang, Z., and Ding, K. (2012). Rh(I)-catalyzed enantioselective hydrogenation of α-substituted ethenylphosphonic acids. J. Am. Chem. Soc. *134*, 12474–12477.

55. Dewhurst, R.D., Neeve, E.C., Braunschweig, H., and Marder, T.B. (2015). Sp^2-sp^3 diboranes: astounding structural variability and mild sources of nucleophilic boron for organic synthesis. Chem. Commun. *51*, 9594–9607.

56. Pietsch, S., Neeve, E.C., Apperley, D.C., Bertermann, R., Mo, F., Qiu, D., Cheung, M.S., Dang, L., Wang, J., Radius, U., et al. (2015). Synthesis, structure, and reactivity of anionic sp^2-sp^3 diboron compounds: readily accessible boryl nucleophiles. Chem. Eur. J. *21*, 7082–7098.

57. Lee, J.-E., and Yun, J. (2008). Catalytic asymmetric boration of acyclic α,β-unsaturated esters and nitriles. Angew. Chem. Int. Ed. *47*, 145–147.

58. Guzman-Martinez, A., and Hoveyda, A.H. (2010). Enantioselective synthesis of allylboronates bearing a tertiary or quaternary B-substituted stereogenic carbon by NHC-Cu-catalyzed substitution reactions. J. Am. Chem. Soc. *132*, 10634–10637.

59. Lee, J.C.H., McDonald, R., and Hall, D.G. (2011). Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds. Nat. Chem. *3*, 894–899.

60. Kobayashi, S., Xu, P., Endo, T., Ueno, M., and Kitanosono, T. (2012). Chiral copper(II)-catalyzed enantioselective boron conjugate additions to α,β-unsaturated carbonyl compounds in water. Angew. Chem. Int. Ed. *51*, 12763–12766.

61. Check, C.T., Jang, K.P., Schwamb, C.B., Wong, A.S., Wang, M.H., and Scheidt, K.A. (2015). Ferrocene-based planar chiral imidazopyridinium salts for catalysis. Angew. Chem. Int. Ed. *54*, 4264–4268.

62. Kubota, K., Osaki, S., Jin, M., and Ito, H. (2017). Copper(I)-catalyzed enantioselective nucleophilic borylation of aliphatic ketones: synthesis of enantioenriched chiral tertiary α-hydroxyboronates. Angew. Chem. Int. Ed. *56*, 6646–6650.

63. During the revision process for this manuscript, Ito et al. reported a related paper: Kojima, R., Akiyama, S., and Ito, H. (2018). A copper(I)-catalyzed enantioselective γ-boryl substitution of trifluoromethyl-substituted alkenes: synthesis of enantioenriched γ,γ-*gem*-difluoroallylboronates Angew. Chem. Int. Ed. *57*, 7196–7199.