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Palladium-catalyzed cross-coupling of *gem*-difluorocyclopropanes with *gem*-diborylalkanes: facile synthesis of a diverse array of *gem*-diboryl-substituted fluorinated alkenes†

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This study introduces an efficacious palladium-catalyzed method for the regioselective and stereoselective cross-coupling of *gem*-difluorinated cyclopropanes with an array of *gem*-diborylalkanes under mild reaction conditions. The innovative methodology facilitates the synthesis of 2-fluoroallylic *gem*-diboronic esters with exceptional *Z*-stereo- and chemo-selectivity. Notably, this protocol extended to the ligand-modulated regio- and stereoselectivity divergence cross-coupling of 1,1-difluoro-2-vinylcyclopropane as a reaction partner. Furthermore, we explore further transformations of the fluorinated *gem*-diboronates, encompassing the oxidation to form ketone and hydrogenation to generate mono-fluorinated alkylated *gem*-diboronate.

Introduction

Organoboronates play a critical role in organic synthesis.[1] Among them, *gem*-diborylalkanes, as a new class of organoboron compounds possess multiple transformable sp^3-hybridized carbon units,[2] have gained prominence in organic synthesis due to their stability and ready availability, serving as versatile intermediates in organic synthesis with valuable applications in materials science and medicinal chemistry. Over the past two decades, significant efforts have been dedicated towards construction and transformation of *gem*-diboron compounds,[3] this includes transition metal-catalyzed or transition metal-free multi-borylation of readily available *gem*-dihalides,[4] alkynes,[5] alkenes,[6] and so on.[7] Additionally, the classic "lithiation-substitution" strategy provided a modular and straightforward route to *gem*-bis(boronates), leveraging readily available 1,1-diborylalkanes.[8] Given the important value of *gem*-diborylalkanes in organic synthesis, the synthesis of multi-functional substituted *gem*-diboron compounds remains an important research topic.

On the other hand, fluorinated compounds have found widespread applications across diverse fields, primarily due to the introduction of fluorine moieties that significantly enhance hydrophobicity and metabolic stability.[9] Recently, *gem*-difluorinated cyclopropanes (*gem*-F_2CPs)[10] an easily accessible fluorinated building block,[11] has undergone diverse metal-catalyzed transformations to fluorinated functional molecules. In 2015, Fu and co-workers pioneered a Pd-catalyzed C–C/C–F activation ring-opening reaction of *gem*-F_2CPs, achieving C–N, C–O, and C–C cross-coupling reactions to produce mono-fluorinated alkenes with high linear selectivity.[12] Since this groundbreaking work, this reaction mode has been extended to a variety of transition metal catalysts (Pd, Ni, Rh, and Co) and nucleophiles afford linear/branched monofluoroalkenes.[13] For example, Li, Lv and co-workers reported the regioselective Pd/NHC-catalyzed ring-opening hydrodefluorination/defluorinative functionalization of *gem*-F_2CPs.[10b,e,13h,j] Xia and co-workers reported the Rh-catalyzed regio-switchable cross-coupling of *gem*-F_2CPs to afford different types of fluorinated compounds.[10d,13g,13i,k,m,r] Recently, our group reported Pd-catalysed cross-coupling of *gem*-F_2CPs with *gem*-diborylalkanes and Cu/Pd bimetallic-catalyzed three-component reaction for synthesizing of boryl-substituted fluorinated alkenes.[14] Despite these advancements, no effective method for the synthesizing of *gem*-diboryl-substituted fluorinated alkenes has been reported until now. Herein, we demonstrate an example of palladium-catalyzed cross-coupling of *gem*-difluorinated cyclopropanes with *gem*-diborylalkanes using LDA as a base to produce *gem*-diboryl-substituted fluorinated alkenes under mild reaction conditions with high stereoselectivity. When 1,1-difluoro-2-

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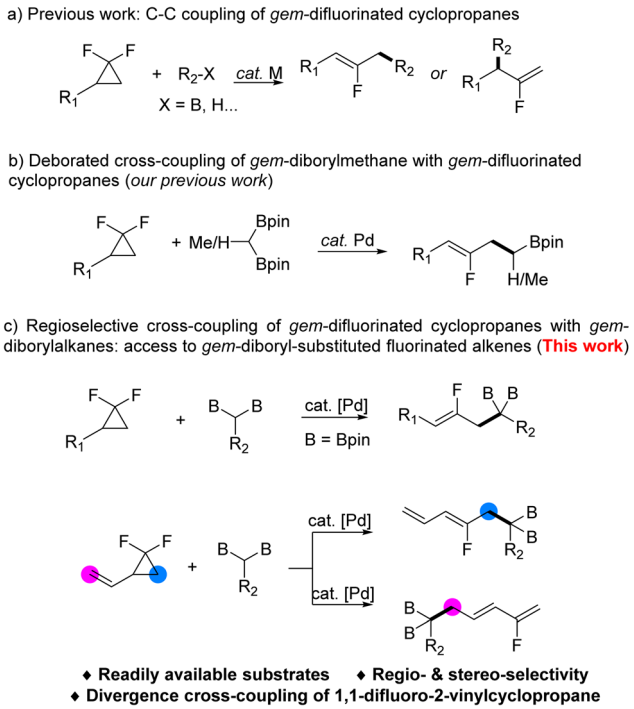


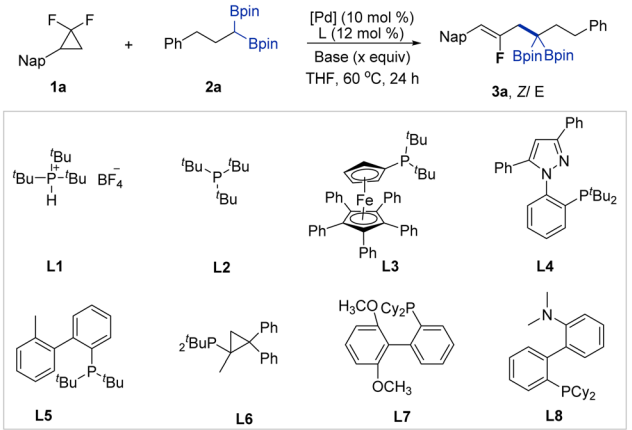
Scheme 1 Transition metal-catalyzed cross-coupling of *gem*-difluorinated cyclopropanes.

vinylcyclopropane is used as the substrate, ligand-modulated regio- and stereoselectivity cross-coupling can be achieved. Incorporating these versatile scaffolds with fluoroallyls, particularly considering the unique properties of fluorine atoms, would enrich the building blocks of *gem*-diborylalkanes (Scheme 1).

Results and discussion

We set out to investigate the cross-coupling reaction using 2-(2,2-difluorocyclopropyl)naphthalene (**1a**) and 2,2′-(3-phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**2a**) as model substrates (Table 1). Based on our prior studies, we initially investigated the impact of phosphorus ligands and Pd catalysts. In the presence of Pd^{II} and LDA, the reaction produced the target product **3a** in low to moderate yields with monodentate ligands (Table 1, entries 1–8). When, switching to Pd^0 catalysts, such as $Pd_2(dba)_3$ and $[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$ along with phosphorus ligands, yields remained moderate but regioselectivity decreased (entries 9, 10). Delightedly, when employing $[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$ in the presence of LDA as the base in THF, **3a** could be obtained in good yield with perfect *Z*-selectivity (28 : 1 *Z*/*E* ratio, entry 11). Subsequently, Buchwald's palladacycle precatalyst controlled the ring-coupling reaction effectively, providing reasonable yield and regioselectivity (entry 15). We also screened a variety of organic and inorganic bases and found that LDA was the most suitable, as other bases were incompatible in the process (entries 12–14, see ESI† for further details). The transformation did not conduct in the absence of LDA or palladium catalyst (entries 16, 17).

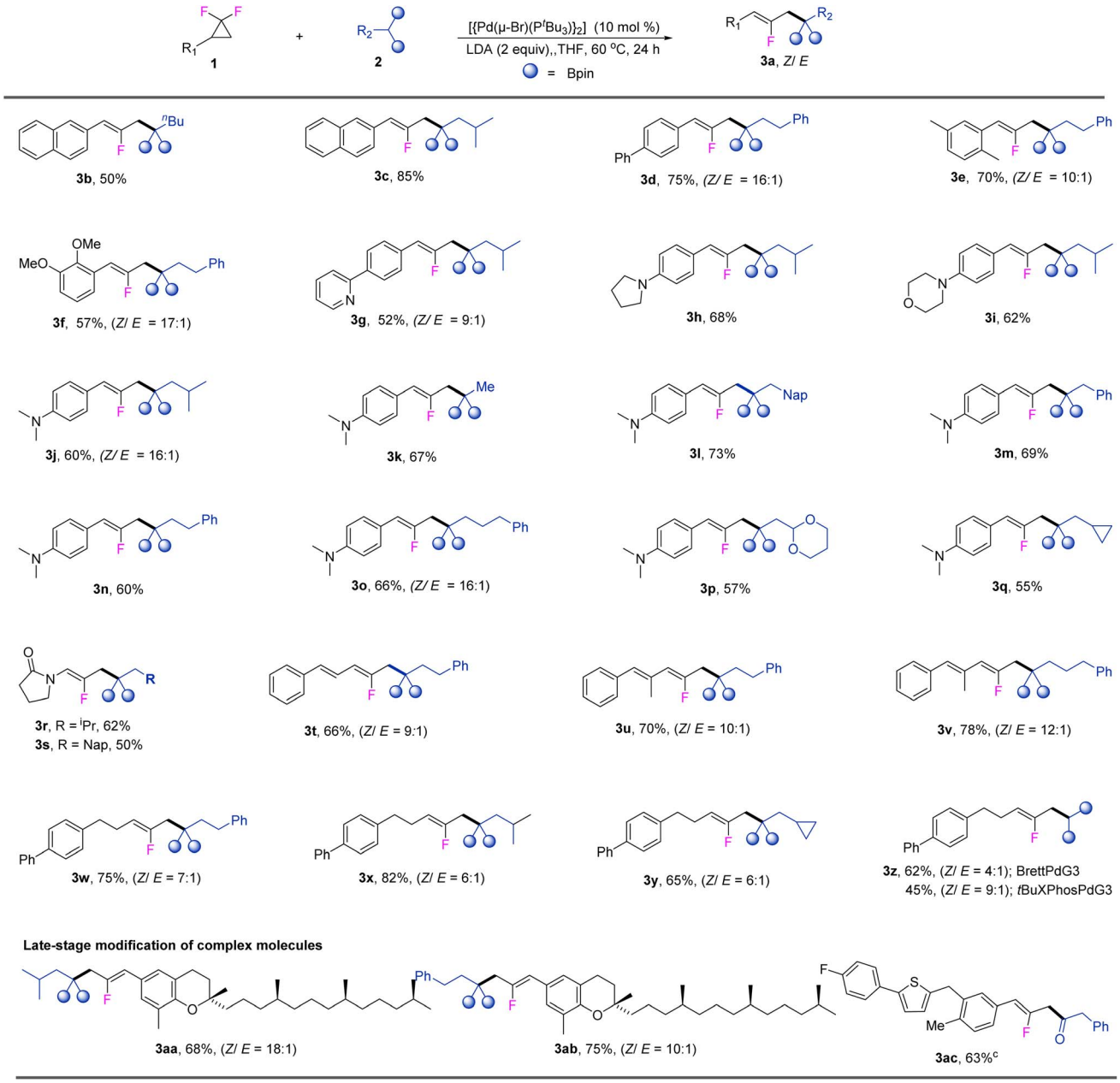
Table 1 Optimization of reaction conditions[a]



Entry	[Pd]	L	Base	Yield[b] (%)	*Z*/*E*[c]
1	$Pd(OTFA)_2$	**L1**	LDA	25	*Z*
2	$Pd(OTFA)_2$	**L2**	LDA	30	*Z*
3	$Pd(OTFA)_2$	**L3**	LDA	35	11 : 1
4	$Pd(OTFA)_2$	**L4**	LDA	46	9 : 1
5	$Pd(OTFA)_2$	**L5**	LDA	65	2 : 1
6	$Pd(OTFA)_2$	**L6**	LDA	61	2 : 1
7	$Pd(OTFA)_2$	**L7**	LDA	13	—
8	$Pd(OTFA)_2$	**L8**	LDA	10	—
9	$Pd_2(dba)_3$	**L5**	LDA	56	2 : 1
10	$[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$	**L5**	LDA	72	3.5 : 1
11	**$[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$**	**—**	**LDA**	**70 (65)[d]**	**28 : 1**
12	$[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$	—	LiO^tBu	n.r.	—
13	$[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$	—	LiHMDS	Trace	—
14	$[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$	—	LTMP	10	—
15	$P^tBu_3PdG\text{-}3$	—	LDA	55	22 : 1
16	$[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$	—	—	n.r.	—
17	—	—	LDA	n.r.	—

[a] Standard reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv.), [Pd] (10 mol%), ligand (12 mol%), base (2 equiv.), in 1.0 mL of THF at 60 °C for 24 h under Ar atmosphere. [b] The yield was determined by ^{19}F NMR using trifluoromethylbenzene as internal standard. For $[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$ and $P^tBu_3PdG\text{-}3$ catalysts, 10 mol% was used. [c] The ratio of *Z*/*E* isomer was determined by ^{19}F NMR spectroscopy. [d] Yield represents isolated yield after purification by silica gel chromatography. dba = dibenzylideneacetone, OTFA = trifluoroacetate. LDA = lithium diisopropylamide. LiHMDS = Lithium bis(trimethylsilyl)amide. LTMP = Lithium tetramethylpiperiddide. Nap = 2-naphthyl.

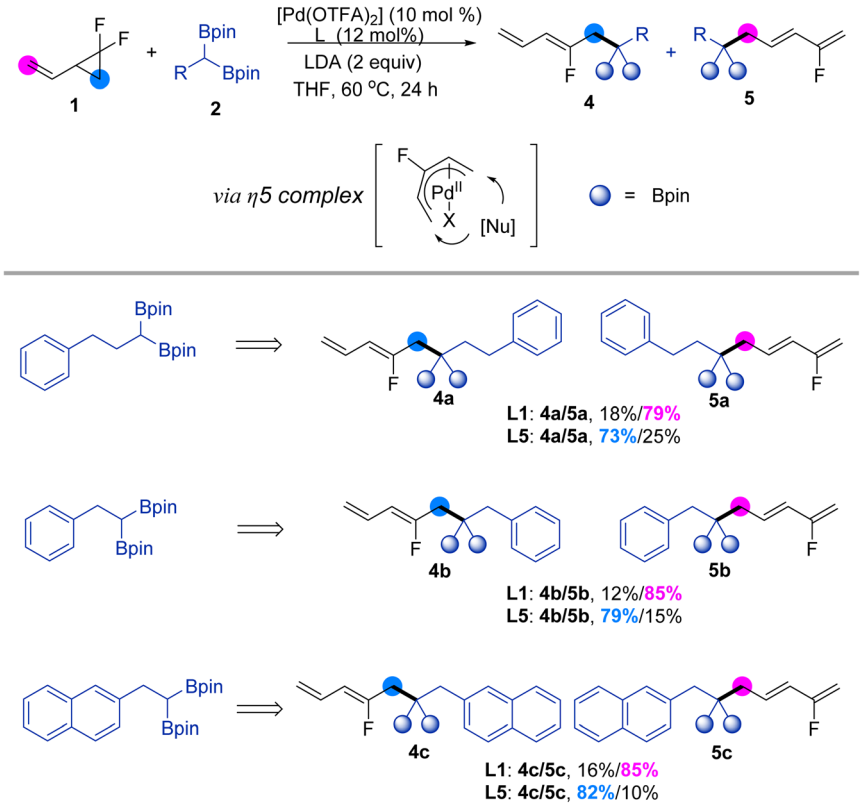
Having established the optimal reaction conditions (as described in Table 1, entry 11), a series of *gem*-F_2CPs and *gem*-diborylalkanes were employed to confirm the generality of the reaction, as depicted in Scheme 2. The ring-coupling proceeded smoothly with neutrally substituted compounds (**3b–3d**) and electron-donating groups at various positions on aromatic rings (**3e**, **3f**), yielding products in the range of 50–85% with reasonable to good regioselectivity. Nitrogen-containing functional groups, such as pyridine, pyrrole, morpholine, dimethylamine substituents, also participated in the reaction with various *gem*-diborylalkanes, furnishing mono-fluorinated *gem*-diborylalkenes (**3g–3o**) in good yields and regioselectivities. Other functional groups, such as acetal (**3p**), pyrrolidinone (**3r**, **3s**),



Scheme 2 Substrate Scope,[a] standard reaction conditions: *gem*-F_2CP **1** (0.2 mmol), *gem*-diborylalkanes **2** (1.5 equiv.), [{Pd(μ-Br)(P^{t}Bu$_3$)}$_2$] (10 mol%), LDA (0.4 mmol), in 2 mL of THF at 60 °C for 24 h under Ar atmosphere.[b] Results are an average of two experiments and yield represents isolated yield after purification by silica gel chromatography, *Z*/*E* selectivity ≥ 20 : 1 unless noted. [c] Oxidant by $NaBO_3 \cdot 4H_2O$ (4 equiv.) after the reaction.

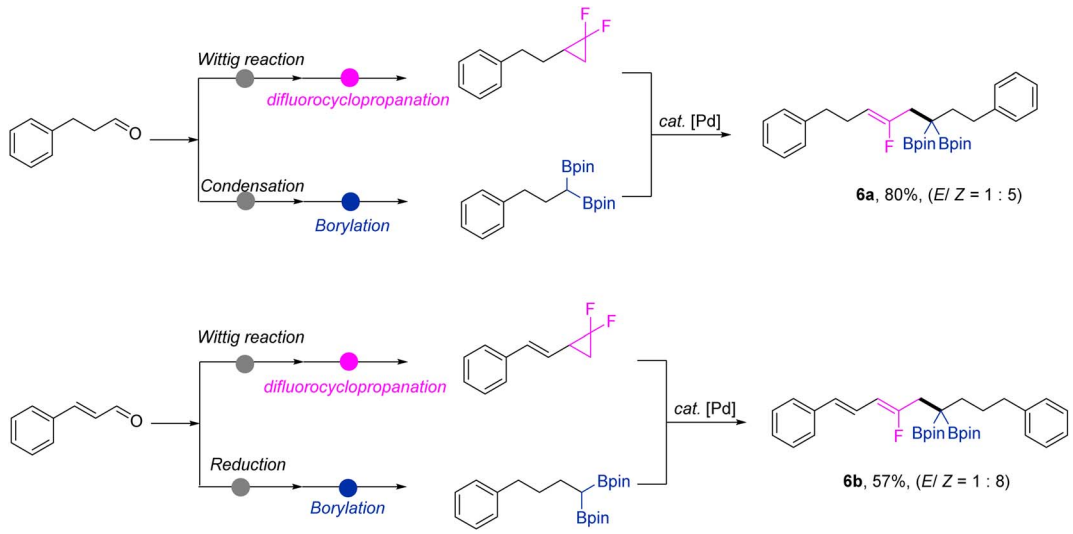
were formed smoothly when *gem*-F_2CPs reacted with *gem*-diboryl derivatives, respectively. Conjugated monofluorinated *gem*-diboronates (**3w–3y**) were synthesized using the corresponding alkenyl *gem*-F_2CPs. To our delight, alkyl-substituted *gem*-F_2CPs were well-tolerated and converted into **3t–3v**. Additionally, the simplest *gem*-diborylmethane also participated in the reaction, yielding **3z** in moderate yield when using Buchwald's precatalysts (*e.g.* BrettPdG3 and ^{t}BuXPhosPdG3) instead of [{Pd(μ-Br)(P^{t}Bu$_3$)}$_2$]. Finally, late-stage modification of complex molecules, such as δ-tocopherol-derived *gem*-F_2CP, was compatible and resulted in yields of **3aa** (68%) and **3ab** (75%). Furthermore, a *gem*-F_2CP-derived canagliflozin participated under optimized conditions, and the corresponding ketone **3ac** was formed *via* a further oxidation step. This approach provides valuable methods for modifying biologically active compounds.

Subsequently, we investigated the scope of *gem*-F_2CPs by performing cross-coupling reactions between 1,1-difluoro-2-vinylcyclopropane and *gem*-diborylalkanes, as illustrated in Scheme 3. By adjusting the optimal conditions, we found that the utilization of a Pd^{II} catalyst, such as Pd(OTFA)$_2$, in combination with difference mono-dentate phosphor ligands, enabled successful regio- and stereoselectivity divergence cross-



Scheme 3 Regio- and stereoselectivities of allyl-*gem*-difluorinated cyclopropane.[a] Standard reaction conditions: 1,1-difluoro-2-vinylcyclopropane (0.2 mmol), *gem*-diborylalkanes (1.5 equiv.), $Pd(OTFA)_2$ (10 mol%), ligand **L1** or **L5** (12 mol%), LDA (0.4 mmol), in 1 mL of THF at 60 °C for 24 h under Ar atmosphere.[b] Results are an average of two experiments and yield represents isolated yield after purification by silica gel chromatography, *Z*/*E* selectivity ≥ 30 : 1 unless noted. **L1** = $P^tBu_3 \cdot HBF_4$, **L5** = di-*tert*-butyl(2′-methyl-[1,1′-biphenyl]-2-yl)phosphane.

coupling. We examined the coupling of 1,1-difluoro-2-vinylcyclopropane with phenylpropane *gem*-diboronates (see ESI† for optimal conditions). For instance, using ligand **L5** led to smooth ring-opening and the formation of **4a** with high stereoselectivity. Interestingly, a flipped ratio products (**4a**/**5a**) was observed when $P^tBu_3 \cdot HBF_4$ (**L1**) was used as the ligand. This trend also proved compatible with other *gem*-diborylalkanes, yielding the corresponding compounds (**4b**, **4c**, **5b**, **5c**) under mild conditions. This represents the first regionally selectively controlled cross-coupling reaction involving 1,1-

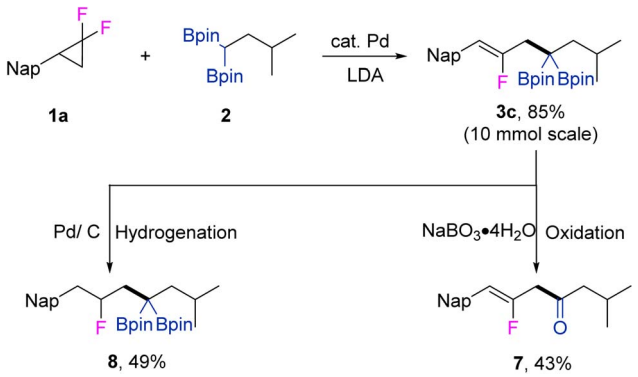


Scheme 4 Easy access C–C coupling reaction toward *gem*-diborylfluorinated alkenes.[a] Isolated yield for 0.2 mmol scale reaction.

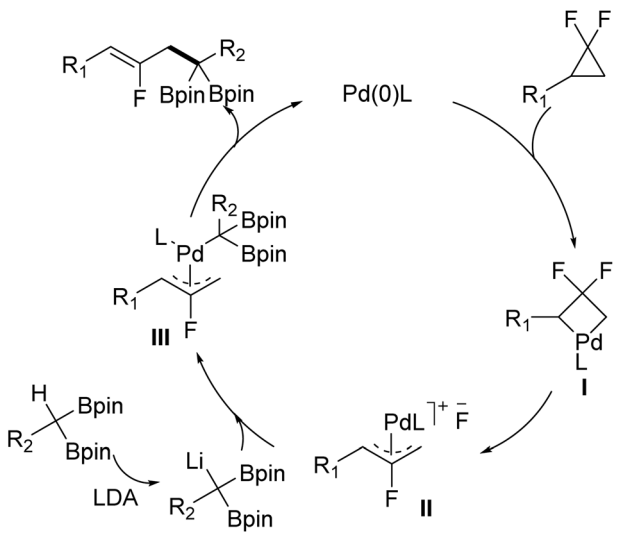
difluoro-2-vinylcyclopropane, thereby broadening the type of difluorocyclopropane ring-opening coupling reaction.

Gem-diborylalkanes and *gem*-difluorocyclopropanes are well-known compounds that can be easily prepared in the laboratory using readily available substrates. Phenylpropanal and cinnamaldehyde, which are biomass-derived feedstocks, can be utilized to synthesize the corresponding *gem*-F_2CPs and *gem*-diborylalkanes. Utilizing our developed method, we achieved the straightforward synthesis of **6a** and **6b** under optimized conditions, yielding the target products in 80% yield and 57% yield, respectively, as illustrated in Scheme 4.

To demonstrate the utility of our cross-coupling method, we performed a gram-scale synthesis of **3c** under standard conditions, resulting in a high yield of **3c** (4.30 g, 85% yield). Furthermore, we explored the potential applications of monofluoroalkene diboronates as a versatile building block. Notably, **3c** was successfully oxidized by $NaBO_3 \cdot 4H_2O$ to yield the corresponding ketone **7** in moderate yield. Additionally, the hydrogenation reaction was carried out to produce monofluoroalkane *gem*-diboronate **8** (Scheme 5).



Scheme 5 Gram-scale synthesis and transformation of mono-fluoroalkene diboronates.[a] For preparation of **3c**, isolated yield for 10 mmol scale reaction; isolated yield for final product of oxidation and hydrogenation reactions were 0.1 mmol scale reaction.



Scheme 6 Proposed reaction mechanism.

The proposed reaction pathway for this strategy is elucidated based on prior studies, as depicted in Scheme 6. Initially, the Pd(0) catalyst interacts readily with *gem*-difluorinated cyclopropanes, leading to the formation of the four-membered-ring palladacycle intermediate (**I**). Subsequently, a β-F elimination step facilitates the generation of the 2-fluorinated Pd π-allyl complex (**II**). This complex then undergoes transmetalation with the *in situ* generated *gem*-diborylalkyl-lithium intermediate, leading to the formation of intermediate (**III**). Finally, a C–C bond elimination assembles the target products, while the Pd catalyst is released for further transformation.

Conclusions

In conclusion, the study demonstrates an instance of Pd-catalyzed ring-opening cross-coupling between *gem*-F_2CPs and *gem*-diborylalkanes to produce *gem*-diboryl-substituted fluorinated alkenes. This reaction proceeds under mild conditions with LDA as the base and exhibits exceptional compatibility with diverse functional groups. Ligand-controlled regio- and stereoselective cross-coupling of 1,1-difluoro-2-vinylcyclopropane can be achieved. This achievement broadens the scope of C–C coupling reactions involving *gem*-F_2CPs and *gem*-diborylalkanes, providing an efficient synthetic route to diverse *gem*-diboronate analogs. Ongoing research focuses on addressing remaining challenges in C–C coupling reactions to further advance this area of work.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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