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Palladium-catalyzed cross-coupling of gemdifluorocyclopropanes with gem-diborylalkanes: facile synthesis of a diverse array of gem-diborylsubstituted 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.

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Introduction

Organoboronates play a critical role in organic synthesis.1 Among them, gem-diborylalkanes, as a new class of organoboron compounds possess multiple transformable sp³-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 gemdihalides,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, gemdifluorinated cyclopropanes (gem-F2CPs)10 an easily accessible fluorinated building block,11 has undergone diverse metalcatalyzed 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-F2CPs, achieving C-N, C-O, and C-C cross-coupling reactions to produce monofluorinated 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-F2CPs. 10b,e,13h,j Xia and co-workers reported the Rh-catalyzed regio-switchable crosscoupling of gem-F2CPs to afford different types of fluorinated compounds. 10d,13g,13i,k,m,r Recently, our group reported Pdcatalysed cross-coupling of gem-F₂CPs 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 palladiumcatalyzed cross-coupling of gem-difluorinated cyclopropanes with gem-diborylalkanes using LDA as a base to produce gemdiboryl-substituted fluorinated alkenes under mild reaction conditions with high stereoselectivity. When 1,1-difluoro-2-

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a) Previous work: C-C coupling of gem-difluorinated cyclopropanes

b) Deborated cross-coupling of *gem*-diborylmethane with *gem*-difluorinated cyclopropanes (*our previous work*)

c) Regioselective cross-coupling of *gem*-difluorinated cyclopropanes with *gem*-diborylalkanes: access to *gem*-diboryl-substituted fluorinated alkenes (This work)

◆ Readily available substrates
 ◆ Regio- & stereo-selectivity
 ◆ Divergence cross-coupling of 1,1-difluoro-2-vinylcyclopropane

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

vinyleyclopropane 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-(2,2difluorocyclopropyl)naphthalene (1a) and 2,2'-(3-phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) model substrates (Table 1). Based on our prior studies, we initially investigated the impact of phosphorus ligands and Pd catalysts. In the presence of PdII 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 Pd⁰ catalysts, such as $Pd_2(dba)_3$ and $[\{Pd(\mu-Br)(P^tBu_3)\}_2]$ along with phosphorus ligands, yields remained moderate but regioselectivity decreased (entries 9, 10). Delightedly, when employing $[\{Pd(\mu-Br)(P^tBu_3)\}_2]$ 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

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	$[\{Pd(\mu-Br)(P^tBu_3)\}_2]$	L5	LDA	72	3.5:1
11	$[\{Pd(\mu-Br)(P^tBu_3)\}_2]$	_	LDA	70 (65) ^d	28:1
12	$[\{\operatorname{Pd}(\mu\operatorname{-Br})(\operatorname{P}^t\operatorname{Bu}_3)\}_2]$	_	${ m LiO}^t{ m Bu}$	n.r.	_
13	$[\{\operatorname{Pd}(\mu\operatorname{-Br})(\operatorname{P}^t\operatorname{Bu}_3)\}_2]$	_	LiHMDS	Trace	_
14	$[\{Pd(\mu-Br)(P^tBu_3)\}_2]$	_	LTMP	10	_
15	P ^t Bu ₃ PdG-3	_	LDA	55	22:1
16	$[\{\operatorname{Pd}(\mu\operatorname{-Br})(\operatorname{P}^t\operatorname{Bu}_3)\}_2]$	_	_	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 ¹⁹F NMR using trifluoromethylbenzene as internal standard. For $[\{Pd(\mu-Br)(P^tBu_3)\}_2]$ and P^tBu_3PdG-3 catalysts, 10 mol% was used. ^c The ratio of Z/E isomer was determined by ¹⁹F NMR spectroscopy. ^d Yield represents isolated yield after purification by silica gel chromatography. dba = dibenzylideneacetone, OTFA = trifluoroacetate. LDA = lithium diisopropylamide. LiHMDS = Lithium bis(trimethylsily)lamide. LTMP = Lithium tetramethylpiperiddide. Nap = 2-naphthyl.

Having established the optimal reaction conditions (as described in Table 1, entry 11), a series of *gem*-F₂CPs 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, standard reaction conditions: gem-F₂CP 1 (0.2 mmol), gem-diborylalkanes 2 (1.5 equiv.), [{Pd(μ-Br)(PtBu₃)}₂] (10 mol%), LDA (0.4 mmol), in 2 mL of THF at 60 °C for 24 h under Ar atmosphere. Besults are an average of two experiments and yield represents isolated yield after purification by silica gel chromatography, Z/E selectivity $\geq 20:1$ unless noted. Coxidant by NaBO₃·4H₂O (4 equiv.) after the reaction.

were formed smoothly when gem-F2CPs reacted with gemdiboryl derivatives, respectively. Conjugated monofluorinated gem-diboronates (3w-3y) were synthesized using the corresponding alkenyl gem-F₂CPs. To our delight, alkyl-substituted gem-F2CPs 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 ^tBuXPhosPdG3) instead of $[\{Pd(\mu-Br)(P^tBu_3)\}_2]$. Finally, late-stage modification of complex molecules, such as δ-tocopherol-derived gem-F₂CP, was compatible and resulted in yields of 3aa (68%) and 3ab (75%).

Furthermore, a gem-F2CP-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.

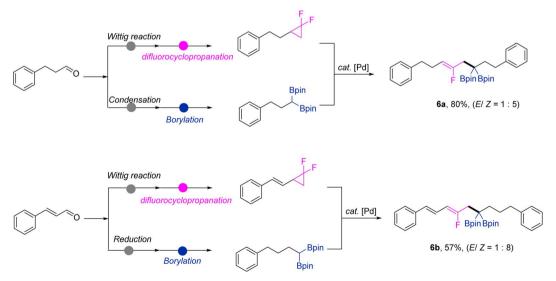
Subsequently, we investigated the scope of gem-F2CPs by performing cross-coupling reactions between 1,1-difluoro-2vinylcyclopropane and gem-diborylalkanes, as illustrated in Scheme 3. By adjusting the optimal conditions, we found that the utilization of a PdII catalyst, such as Pd(OTFA)2, in combination 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-vinyl-cyclopropane (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 $\geq 30:1$ unless noted. L1 = $P^tBu_3 \cdot HBF_4$, L5 = di-tert-butyl(2'-methyl-[1,1'-biphenyl]-2-yl)phosphane.

L5: 4c/5c, 82%/10%

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. 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-F₂CPs 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 NaBO₃·4H₂O to yield the corresponding ketone 7 in moderate yield. Additionally, the

Scheme 5 Gram-scale synthesis and transformation of mono-fluo-roalkene 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.

hydrogenation reaction was carried out to produce monofluoroalkane *gem*-diboronate 8 (Scheme 5).

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 Pdcatalyzed ring-opening cross-coupling between gem-F2CPs 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 1,1-difluoro-2of vinylcyclopropane can be achieved. This achievement broadens the scope of C-C coupling reactions involving gem-F2CPs 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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