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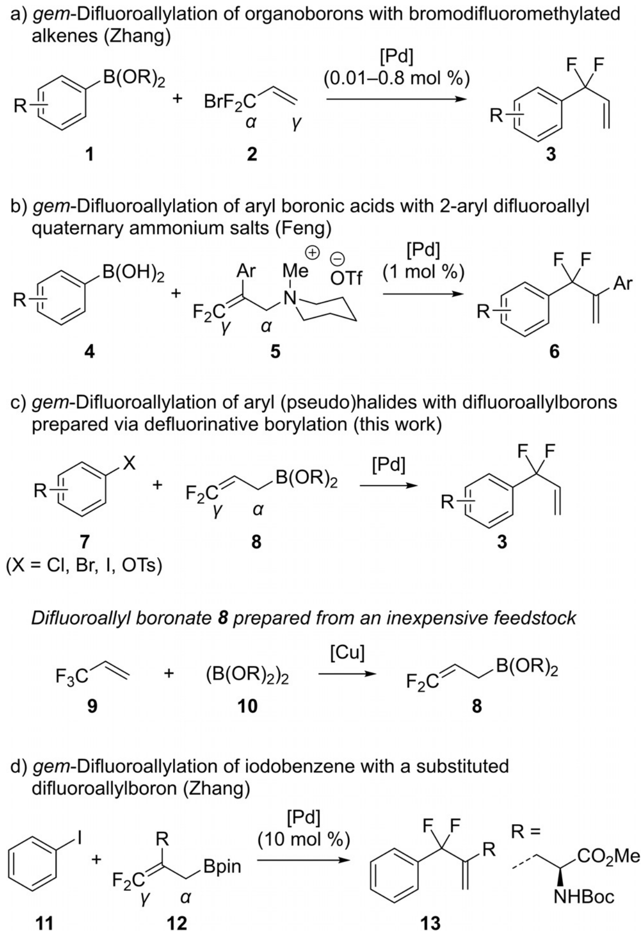
gem-Difluoroallylation of Aryl Halides and Pseudo Halides with Difluoroallylboron Reagents in High Regioselectivity

Shu Sakamoto, Trevor W. Butcher[+]*, Jonathan L. Yang*[+]*, and John F. Hartwig**

Abstract: *We report the palladium-catalyzed gem-difluoroallylation of aryl halides and pseudo halides with 3,3-difluoroallyl boronates in high yield with high regioselectivity, and we report the preparation of the 3,3-difluoroallyl boronate reactants by a copper-catalyzed defluorinative borylation of inexpensive gaseous 3,3,3-trifluoropropene with bis(pinacolato)diboron. The gem-difluoroallylation of aryl and heteroaryl bromides proceeds with low catalyst loading (0.1 mol% [Pd]) and tolerates a wide range of functional groups, including primary alcohols, secondary amines, ethers, ketones, esters, amides, aldehydes, nitriles, halides, and nitro groups. This protocol extends to aryl iodides, chlorides, and triflates, as well as substituted difluoroallyl boronates, providing a versatile synthesis of gem-difluoroallyl arenes that we show to be valuable intermediates to a series of fluorinated building blocks.*

The difluoromethylene (CF_2) unit can be used to fine-tune the physical, chemical, and biological properties of pharmaceuticals, agrochemicals, and materials.[1] This unit can serve as a bioisostere for an ether linkage or a keto group in pharmaceuticals,[2] and, when positioned at a benzylic site, it can block metabolic oxidation at otherwise labile benzylic C–H bonds.[2] Difluoromethylene groups also have been used to alter the lipophilicity and ground-state conformation of organic molecules.[2] Compounds containing difluoromethylene groups even serve as valuable reactants, for example undergoing C–F bond activation during reactions that form alkyl fluorides.[3]

However, the installation of a difluoromethylene group poses synthetic challenges. Classical approaches to access 1,1-difluoroalkanes, such as the deoxyfluorination of ketones with DAST or Deoxo-Fluor®,[4] the fluorodesulfurzation of dithianes,[5] and the hydrofluorination of alkynes,[6,7] typically proceed in low yield and exhibit poor functional group tolerance. Recently, difluoroalkylations catalyzed by transition-metal complexes have provided an alternative, convergent route to access compounds containing the difluoromethylene group.[8] Among these, difluoroallylations are notable for their ability to simultaneously install a difluoromethylene group and a versatile alkene functional group. In 2014, Zhang et al. reported the palladium-catalyzed coupling of arylboron reagents **1** and 3-bromo-3,3-difluoropropene (**2**) to provide synthetically versatile *gem*-difluoroallyl arenes **3** (Scheme 1a).[9] Similarly, Feng et al. demonstrated that aryl boronic acids **4** undergo cross-coupling with 2-aryl difluoroallyl quaternary ammonium salts **5** to provide 2-aryl difluoroallyl arenes **6** (Scheme 1b).[10] However, the arylboron reagents used in these reactions as the source of the aryl group are much less available than aryl halides and the 3-bromo-3,3-difluoropropene reagent used as the source of the difluoroallyl group in one protocol is expensive;[11] it is prepared from dibromodifluoromethane and ethylene by



Scheme 1. Background on the difluoroallylation of aromatic compounds.

[*] S. Sakamoto, T. W. Butcher,[+] J. L. Yang,[+] Prof. J. F. Hartwig
Department of Chemistry, University of California
Berkeley, California 94720 (USA)
E-mail: jhartwig@berkeley.edu
S. Sakamoto
Material Science Research Laboratory, Kao Corporation
Wakayama, Wakayama Prefecture 640-8580 (Japan)
[+] These authors contributed equally to this work.

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a two-step, gas-phase synthesis requiring an autoclave system.[12] The 2-aryl difluoroallyl quaternary ammonium salts applied by Feng require an equivalent amount of alkyl lithium reagent for their preparation. Thus, the coupling of an aryl halide with a difluoroallyl reagent that is derived from an abundant organofluorine compound is needed for difluoroallylation to be widely adopted.

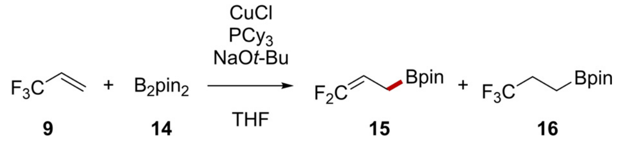
We envisioned that the cross-coupling of an aryl halide or pseudo halide **7** (and the heteroaryl analogs) with a 3,3-difluoroallyl boronate **8** to form *gem*-difluoroallyl arenes **3** would be an expedient, affordable, and versatile route to *gem*-difluoroallyl arenes. This process (Scheme 1c) would occur between widely available, readily accessible aryl halides or pseudo halides[13] and difluoroallyl boronates, which could be prepared by the defluorinative borylation of the inexpensive, gaseous 3,3,3-trifluoropropene (**9**),[14] or substituted trifluoromethyl alkenes. Thus far, just one example of the cross-coupling of an aryl halide with a substituted 3,3-difluoroallyl boronate has been reported (Scheme 1d),[15] and this example required iodide as leaving group on the arene, occurred in modest yield (55%), and required high catalyst loadings (10 mol% [Pd]).

Herein, we report the palladium-catalyzed *gem*-difluoroallylation of aryl chlorides, bromides, iodides, and triflates with difluoroallylboron reagents synthesized from 3,3,3-trifluoropropene (Scheme 1c) or substituted trifluoromethyl alkenes. These reactions proceed with low catalyst loadings in high yields with high regioselectivities. The products undergo a wide range of transformations without defluorination to form building blocks containing the combination of a difluoromethylene unit at the benzylic position and a wide array of functional groups.

To achieve the target difluoroallylation reaction, we first developed a practical preparation of 3,3-difluoroallyl pinacol boronate (**15**) from 3,3,3-trifluoropropene (**9**). Ramachandran et al. previously reported the synthesis of 3,3-difluoroallyl diisopropyl boronate by the homologation of 2,2-difluorovinyllithium with diisopropyl iodomethylboronate; however, this route required an expensive iodomethylboron reagent and stoichiometric organolithium reagents.[16] Therefore, we sought to develop an alternative synthesis of 3,3-difluoroallyl boronates.

We investigated the defluorinative borylation of 3,3,3-trifluoropropene (**9**) catalyzed by copper(I) chloride and tricyclohexylphosphine, based on previous reports of the copper-catalyzed defluorinative borylation of trifluoromethyl- or difluoromethyl-substituted alkenes.[17,18] By conducting the defluorinative borylation of gaseous trifluoropropene **9** in a sealed, pressurized flask at low temperatures, the desired boronate **15** was produced in 71% yield (Table 1, entry 1). However, alkyl boronate **16**, derived from the hydroboration of trifluoropropene **9**, was observed in 11% yield. Formation of this side product was suppressed by conducting the reaction with a larger amount of NaO*t*-Bu. The reaction with 1.0 equiv instead of 0.4 equiv of NaO*t*-Bu formed difluoroallyl boronate **15** without the formal hydroboration product **16** (entry 2). Furthermore, reactions conducted with 5.0 mol% of the copper catalyst proceeded in higher yield than reactions conducted with 20 mol% of the copper catalyst (entry 3). We note that 3,3-difluoroallyl pinacol boronate (**15**) is bench-stable for months, in contrast to the 3,3-difluoroallyl diisopropyl boronate previously reported by Ramachandran et al., which is unstable and must be used immediately after it is prepared.[16]

Table 1: Preparation of 3,3-difluoroallyl pinacol boronate.[a]

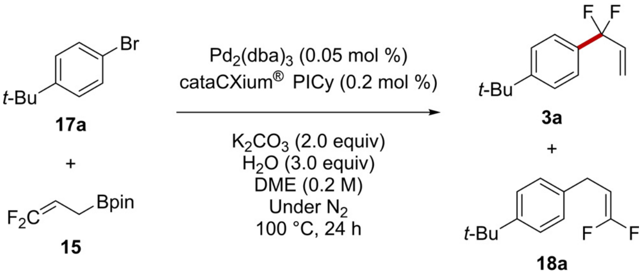


Entry	CuCl [mol%]	PCy_3 [mol%]	NaO*t*-Bu (equiv)	Yield [%] **15**	**16**
1	20	20	0.4	71	11
2	20	20	1.0	79	<1
3	5.0	5.0	1.0	89 (77[b])	<1

[a] Reaction conditions: **9** (ca. 250–300 mL), **14** (5.87 mmol, 1 equiv), CuCl (5.0–20 mol%), PCy_3 (5.0–20 mol%), NaO*t*-Bu (0.4–1.0 equiv), THF (12 mL, 0.5 M), −78°C, 1 h; 0°C to RT, 16 h. All reported yields were determined by ^{19}F NMR with 1,4-difluorobenzene as the internal standard. [b] The number in parentheses is combined isolated yields of **15** and **16**, and the ratio of **15/16** was >99:1.

Our initial efforts to develop the *gem*-difluoroallylation of aryl halides and pseudo halides focused on the reaction of 4-*tert*-butylbromobenzene (**17a**) with 3,3-difluoroallyl pinacol boronate (**15**). We investigated a variety of palladium catalysts and commercially available phosphine ligands with high-throughput experimentation techniques (see SI for details). CsF and Cs_2CO_3 were selected as the bases for these experiments because the former is commonly used for the coupling reactions between aryl bromides and allyl pinacol boronate,[19] and the latter was shown to lead to formation of the coupled product in preliminary studies. Reactions conducted with the combination of $Pd_2(dba)_3$ and cataCXium® PCy proceeded with full conversions of **17a** and excellent yields of **3a**. Among the commercially available cataCXium® P ligands investigated, cataCXium® PICy formed a catalyst that generated the product in high yield with the highest regioselectivity. Reactions conducted with this ligand proceeded in 88% yield of **3a** and >99:1 selectivity for **3a** over **18a** under conditions with just 0.1 mol% of palladium (Table 2, entry 2). Reactions with K_2CO_3, a base that is less expensive and more suitable for scale-up than Cs_2CO_3, occurred in equivalent yields with 1.0 mol% of palladium. Reactions conducted with $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ as the catalyst also were shown by the high-throughput experiments to form substantial amounts of product, but reactions with these catalysts proceeded in lower yield than those conducted with the combination of $Pd_2(dba)_3$ and cataCXium® PICy (entries 3–5). The use of a ligand and a base was essential for the reaction, and, although the use of an inert atmosphere was also important for high yields (entries 6–8), reactions with added water occurred with just 0.1 mol% of catalyst with K_2CO_3 as base while maintaining a high yield and high γ-selectivity (entries 1, 9). The *gem*-difluoroallylation of aryl bromide **17a** proceeded in excellent yield with exclusive γ-selectivity when conducted on a gram scale, provided it was conducted in 1,4-dioxane instead of DME (entry 11).

Table 2: Representative results for the optimization of *gem*-difluoroallylation of 4-*tert*-butylbromobenzene with difluoroallyl boronate.[a]



Entry	Variations from above	Yield [%] 3a + 18a	Ratio 3a/18a
1	None	94	>99:1
2[b]	Cs_2CO_3 (1.1 equiv) as the base	88	>99:1
3[b,c]	$Pd_2(dba)_3$ (0.5 mol%) cataCXium® PICy (2.0 mol%)	92	>99:1
4[b,c,d]	$Pd(PPh_3)_4$ (1.0 mol%) as the catalyst	51	29:1
5[b,c,d]	$Pd(dppf)Cl_2$ (1.0 mol%) as the catalyst	54	>99:1
6	Without cataCXium® PICy	n.r.	-
7	Without K_2CO_3	n.r.	-
8	Under air	n.r.	-
9	Without H_2O	70	56:1
10[e]	None	(97)	>99:1
11[f]	1,4-Dioxane as the solvent	(99)	>99:1

[a] Reaction conditions: **17a** (0.04 mmol, 1.0 equiv), **15** (0.048–0.060 mmol, 1.2–1.5 equiv), DME (0.2 mL). All reported yields are combined yields of **3a** and **18a**, and were determined by ^{19}F NMR with 1,4-difluorobenzene as the internal standard. All reported yields in parentheses are the combined isolated yields of **3a** and **18a**. The ratio of **3a/18a** was determined by ^{19}F NMR before workup. [b] Concentration was 0.125 M. H_2O was not used. [c] 3.0 equiv of K_2CO_3 was used. Reaction run at 80 °C. [d] $Pd_2(dba)_3$ and cataCXium® PICy were not used. [e] 100 mg scale. [g] 1.5 g scale. n.r. = no reaction.

With conditions for the *gem*-difluoroallylation of aryl bromides identified, we investigated the scope of aryl bromides that undergo this transformation (Table 3). Aryl bromides bearing a wide range of functional groups, including vinyl, primary alcohol, secondary amine, aldehyde, nitrile, ketone, ester, amide, nitro, and TIPS-protected alkyne underwent difluoroallylation in high yield (**3d**–**3l**, **3o**, **3t**). The difluoroallylation of *para*-bromo benzaldehyde (**17g**) proceeded in good yield and selectivity (**3g**); however, minor products containing a benzyl alcohol or carboxylic acid functional group were also obtained, likely resulting from a competitive Cannizzaro reaction. Bromoarenes bearing a phenyl substituent situated at the *para*, *meta*, and *ortho* position all underwent difluoroallylation in high yield and selectivity (**3c**, **3u**, **3y**). Pentamethyl bromobenzene (**17s**), a sterically hindered, electron-rich aryl bromide possessing two *ortho* substituents, underwent *gem*-difluoroallylation in high yield as well (**3s**). Electronically biased bromoarenes also underwent difluoroallylation in high yield. For example, bromoarenes bearing both strongly electron-withdrawing (NO_2, CN) and strongly electron-donating substituents (OBn, NHBoc) at the *para* position underwent difluoroallylation in excellent yield (**3h**, **3m**–**3o**).

The difluoroallylation of bromoarenes bearing two different halides or one halide and one pseudo halide occurred with excellent selectivity for one halide over the other. For example, the difluoroallylation of both *para*-bromo phenyl chloride and *para*-bromo phenyl triflate occurred exclusively at the bromide (**3p**, **3q**).

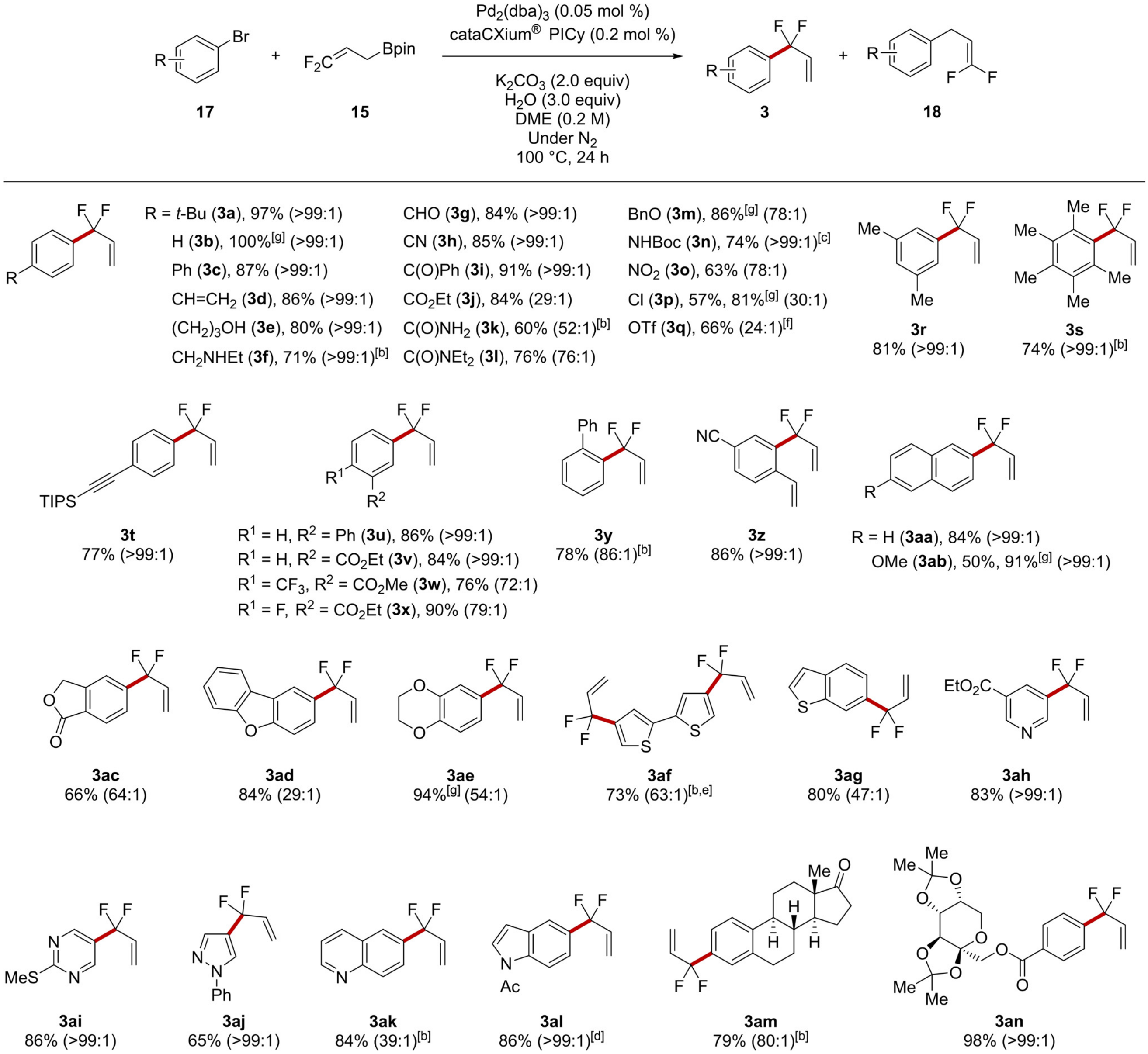
This protocol also led to the difluoroallylation of a variety of heterocyclic halides relevant to medicinal chemistry, including those containing oxygen, sulfur, and nitrogen. For example, 4,4′-dibromo-2,2′-bithiophene underwent difluoroallylation to provide the difunctionalized product **3af**, and 6-bromobenzo[*b*]thiophene underwent *gem*-difluoroallylation in high yield under the standard conditions (**3ag**). A pyridyl bromide, which could not be converted into the cross-coupled product by reaction of a pyridylboron reagent,[9] reacted smoothly to provide the difluoroallylated pyridine **3ah** in high yield and selectivity. The *gem*-difluoroallylation of other nitrogen-containing heteroaryl bromides such as bromopyrimidines and bromopyrazoles also proceeded in high yield and selectivity (**3ai**–**3al**), and aryl bromides featuring a steroid or carbohydrate motif underwent difluoroallylation in high yield and excellent regioselectivity (**3am**, **3an**).

Substituted difluoroallyl boronates also served as coupling partners to form difluoroallyl arenes (Table 4). These reagents were prepared by iron- or copper-catalyzed defluorinative borylation of the corresponding trifluoromethyl compounds.[17b,c] Although the cross-couplings of β-substituted difluoroallyl boronates required extended reaction times (48 hours), high yields and selectivities were achieved (**20a**–**20g**). An α-substituted difluoroallyl boronate underwent cross-coupling at a similar rate to unsubstituted difluoroallyl pinacol boronate **15** to provide the linear difluorobenzyl alkene **20h** as a mixture of geometric isomers in high yield; however, difluoroallyl pinacol boronates bearing substituents at both α and β positions were unreactive (see SI for details).

Aryl iodides and chlorides, as well as aryl triflates, also underwent efficient *gem*-difluoroallylation (Table 5). The difluoroallylation of aryl iodides proceeded in higher yield when conducted with anhydrous Cs_2CO_3 than with the combination of K_2CO_3 and water. Under these conditions with Cs_2CO_3, aryl iodides underwent cross-coupling in excellent yield and selectivity with just 0.1 mol% of palladium (Table S5). To our surprise, the cross-coupling of aryl chlorides was inhibited by potassium chloride, a byproduct formed throughout the reaction (Table S6). To overcome this inhibition by chloride, the cross-coupling of aryl chlorides was conducted in anhydrous toluene, a solvent in which potassium chloride is insoluble. To ensure complete conversion within 48 hours, the cross-coupling of aryl chlorides was conducted with 1.0 mol% palladium. Finally, aryl triflates underwent difluoroallylation in excellent yield and selectivity under the reaction conditions developed for aryl chlorides (Table S7). We expect the compatibility of the present transformation with four different halides and pseudo halides (Cl, Br, I, and OTf) will make this method widely applicable for the synthesis of difluoroallyl arenes and difluoroallyl heteroarenes.

1,1-Difluoroallyl arenes are versatile synthetic intermediates because alkenes undergo a myriad of transformations. However, the chemistry of these difluoroalkylated alkenes, which are strongly electronically biased and possess poten-

Table 3: Scope of *gem*-difluoroallylation of (hetero)aryl bromides with difluoroallyl boronate.[a]

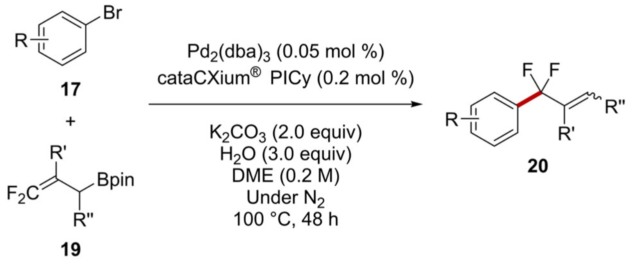


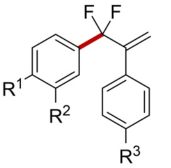
[a] Reaction conditions (unless otherwise specified): **17** (0.5 mmol, 1.0 equiv), **15** (0.6 mmol, 1.2 equiv), $Pd_2(dba)_3$ (0.05 mol%), cataCXium® PICy (0.2 mol%), K_2CO_3 (2.0 equiv), H_2O (3.0 equiv), DME (2.5 mL, 0.2 M), under N_2, 100 °C, 24 h. All reported yields are combined isolated yields of **3** and **18**. The ratio of **3**/**18** in parentheses was determined by ^{19}F NMR before workup. [b] Reaction run at 120 °C. [c] Reaction run at 90 °C. [d] Reaction run at 70 °C for 48 h. [e] 0.25 mmol of **17** (0.5 mmol as Br) was used. [f] **17** (0.5 mmol, 1.0 equiv), **15** (0.6 mmol, 1.2 equiv), $Pd_2(dba)_3$ (0.1 mol%), cataCXium® PICy (0.4 mol%), K_2CO_3 (3.0 equiv), Toluene (2.5 mL, 0.2 M), 100 °C, 48 h. [g] Yields were determined by ^{19}F NMR with 1,4-difluorobenzene as the internal standard before workup.

tially labile C−F bonds, has not been charted. We began by investigating several classical reactions of alkenes (Scheme 2). Hydrogenation of **3aa** provided 1,1-difluoropropyl arene **24** in excellent yield without competing hydrogenolysis of a C−F bond, hydroboration and oxidation of **3u** provided alcohol **25** in high yield with high regioselectivity, reductive ozonolysis of **3u** provided alcohol **26** in moderate yield, and epoxidation of **3a** provided fluorinated epoxide **27** in high yield. Epoxide **27** underwent ring-opening with either lithium aluminium hydride to provide secondary alcohol **28** or *N*-benzylmethylamine to provide fluorinated β-amino alcohol **29**. In prior work, Zhang et al. demonstrated that 1,1-difluoroallyl arenes undergo dihydroxylation in high yield (**30**).[9]

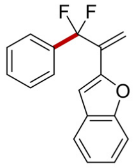
In addition to these classical reagent-based reactions, we investigated several catalytic reactions at the alkene of the difluoroallyl products. 1,1-Difluoroallyl arene **3c** underwent rhodium-catalyzed hydroformylation[20] in 70 % yield with excellent selectivity for the linear product **31**. The resulting aldehyde **31** smoothly underwent oxidation to carboxylic acid **32**, an analogue of the nonsteroidal anti-inflammatory drug Fenbufen. In addition, difluoroallyl arene **3a** underwent

Table 4: Scope of *gem*-difluoroallylation of aryl bromides with substituted difluoroallyl boronates.[a]

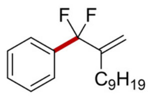




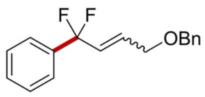
$R^1 = R^2 = R^3 = H$ (**20a**), 81% (>99:1)
$R^1 = CH{=}CH_2$, $R^2 = R^3 = H$ (**20b**), 82% (>99:1)
$R^1 = Cl$, $R^2 = R^3 = H$ (**20c**), 65% (61:1)
$R^1 = R^2 = H$, $R^3 = t\text{-Bu}$ (**20d**), 95% (>99:1)
$R^1 = H$, $R^2 = CO_2Et$, $R^3 = CO_2Me$ (**20e**), 63% (>99:1)



20f
69% (>99:1)



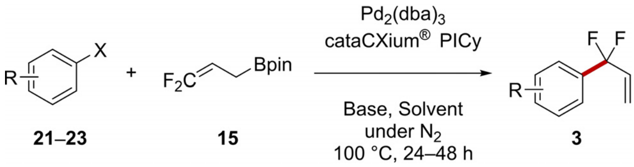
20g
90% (>99:1)



20h
90%, *E*/*Z* = 1:1 (>99:1)[b]

[a] Reaction conditions (unless otherwise specified): **17** (0.5 mmol, 1.0 equiv), **19** (0.6 mmol, 1.2 equiv), $Pd_2(dba)_3$ (0.05 mol%), cataCXium® PICy (0.2 mol%), K_2CO_3 (2.0 equiv), H_2O (3.0 equiv), DME (2.5 mL, 0.2 M), under N_2, 100°C, 48 h. All reported yields are combined isolated yields of γ (**20**) and α. The ratio of γ (**20**)/α in parentheses was determined by ^{19}F NMR before workup. [b] Reaction run for 24 h.

Table 5: Scope of *gem*-difluoroallylation of other electrophiles with difluoroallyl boronate.[a]



X=		I (**21**)	Cl (**22**)	OTf (**23**)
Substrate	*R* = 4-*t*-Bu	71% (> 99:1)	89% (22:1)	63% (24:1)[b]
	R = 4-CO_2Et	82% (78:1)	98% (26:1)	93% (38:1)[c]
$Pd_2(dba)_3$ [mol%]		0.05	0.5	0.5–1.25
cataCXium® PICy [mol%]		0.2	2.0	2.0–5.0
Base		Cs_2CO_3 (1.1 equiv)	K_2CO_3 (3.0 equiv)	K_2CO_3 (3.0 equiv)
Solvent		DME	Toluene	Toluene

[a] Reaction conditions: **21–23** (0.5 mmol, 1.0 equiv), **15** (0.6 mmol, 1.2 equiv), under N_2. All reported yields are combined yields of **3** and **18**, and were determined by ^{19}F NMR with 1,4-difluorobenzene as the internal standard. The ratio of **3**/**18** was determined by ^{19}F NMR. [b] 1.25 mol% of $Pd_2(dba)_3$ and 5.0 mol% of cataCXium® PICy were used. [c] 0.5 mol% of $Pd_2(dba)_3$ and 2.0 mol% of cataCXium® PICy were used.

a palladium-catalyzed Mizoroki–Heck reaction[21] with 4-bromobenzaldehyde to provide **33** in 79% yield with 10:1 *E*/*Z* selectivity. This Mizoroki–Heck reaction outcompetes formation of a π-allyl complex by C–F activation.[22] Difluoro indene **34** formed in moderate yield from the ring-closing metathesis of **3z** with the Grubbs-Hoveyda 2nd generation catalyst, and this product could be a precursor to known bioactive molecules.[23]

In addition to these newly reported reactions, we have previously demonstrated that 1,1-difluoroallyl arenes undergo iridium-catalyzed enantioselective substitution of one fluorine to provide tertiary alkyl fluorides in high yield and high enantioselectivity (**35**, **36**).[24] In addition, we have demonstrated that terminal 1,1-difluoroallyl arenes undergo copper-catalyzed defluorinative borylation and silylation with excellent *Z* selectivity (**37**),[18b] and Ito and Hoveyda et al. have demonstrated that internal 1,1-difluoroallyl arenes undergo defluorinative borylation in excellent yield, with high *Z* selectivity, and high enantioselectivity (**38**).[18a] Collectively, these studies show that the 1,1-difluoroallyl arenes prepared by our new coupling reaction can serve as versatile building blocks to construct more complex, value-added organofluorine compounds.

In summary, we have developed a catalytic method for the *gem*-difluoroallylation of a wide range of aryl and heteroaryl halides and pseudo halides with a bench-stable 3,3-difluoroallyl pinacol boronate (**15**), which we prepared from the inexpensive hydrofluorocarbon 3,3,3-trifluoropropene (**9**). High yields and regioselectivities have been achieved with the combination of $Pd_2(dba)_3$ and cataCXium® PICy at low loadings (0.1–2.5 mol% [Pd]). Various aryl and heteroaryl bromides, as well as aryl chlorides, iodides, and triflates, underwent cross-coupling. We anticipate that this method will be valuable for the synthesis of pharmaceutical candidates and will provide an entry point to new fluorinated building blocks for the development of new synthetic methods.

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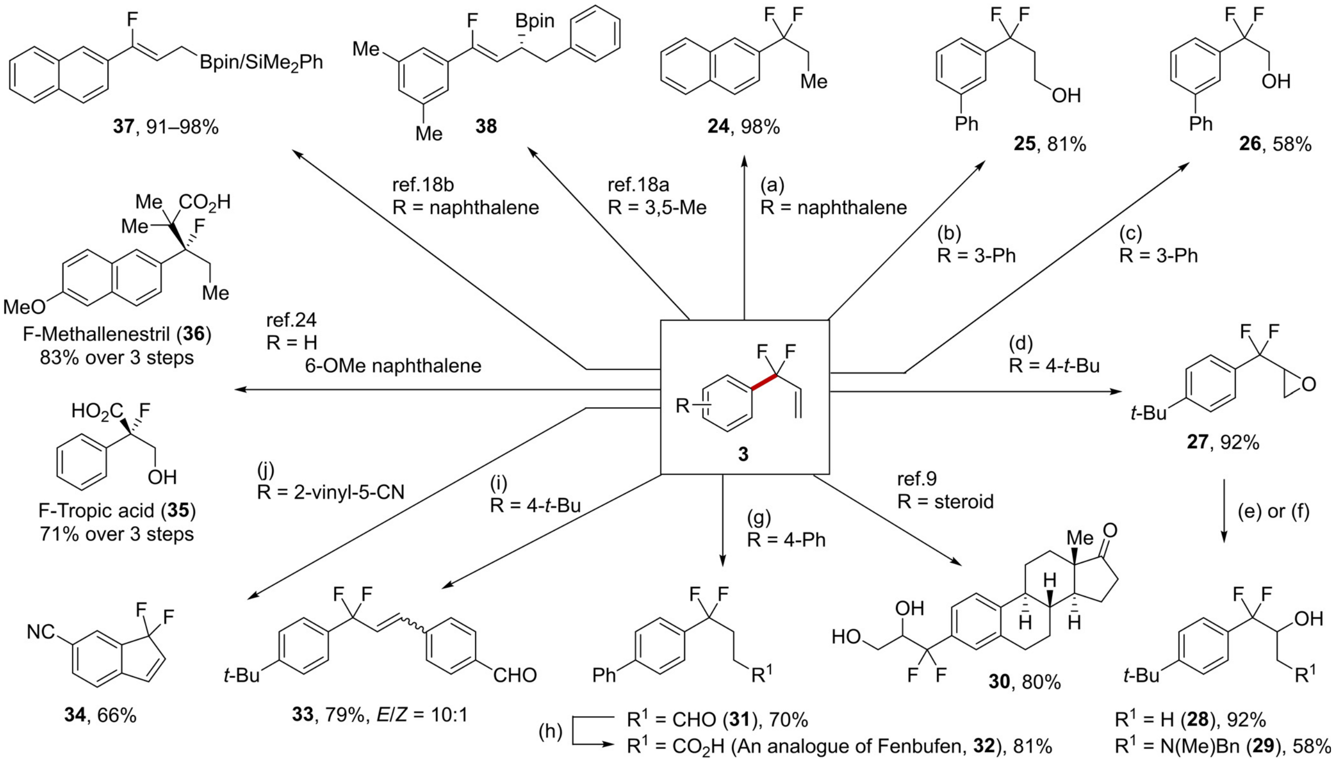
Conflict of Interest

The authors declare no conflict of interest.



Scheme 2. Transformations of *gem*-difluoroallyl arenes. Reaction conditions: a) Pd/C, H_2, EtOAc, RT, 0.75 h. b) 9-BBN, THF, 50 °C, 24 h; aq. NaOH, aq. H_2O_2, RT, 24 h. c) O_3, DCM, −78 °C; $NaBH_4$, −78 °C to RT, 4 h. d) in situ TFDO, MeCN, 0 °C, 4 h. e) $LiAlH_4$, THF, RT, 0.5 h. f) *N*-Benzylmethylamine, K_2CO_3, MeOH, 65 °C, 1.5 h. g) $[Rh(cod)OH]_2$, Xantphos, $CO/H_2 = 1:1$, DMF, 80 °C, 24 h. h) Oxone®, DMF, RT, 5 h. i) 4-Bromobenzaldehyde, $Pd(OAc)_2$, $P(o\text{-tol})_3$, NaOAc, DMF, 125 °C, 6 h. j) Hoveyda–Grubbs 2nd generation catalyst, DCM, 50 °C, 48 h.

Keywords: aryl (pseudo)halides · defluorinative borylation · difluoroallyl boronates · *gem*-difluoroallylation · palladium catalysis

[1] a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; c) Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov, S. Saphier, *J. Med. Chem.* **2019**, *62*, 5628.

[2] a) M. O. Anderson, J. Zhang, Y. Liu, C. Yao, P.-W. Phuan, A. S. Verkman, *J. Med. Chem.* **2012**, *55*, 5942; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315; c) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822.

[3] a) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119; b) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen, Y. Guo, *J. Fluorine Chem.* **2015**, *179*, 14; c) J.-D. Hamel, J.-F. Paquin, *Chem. Commun.* **2018**, *54*, 10224; d) T. Fujita, K. Fuchibe, J. Ichikawa, *Angew. Chem. Int. Ed.* **2019**, *58*, 390; *Angew. Chem.* **2019**, *131*, 396.

[4] a) L. N. Markovsij, V. E. Pahinnik, A. V. Kirsanov, *Synthesis* **1973**, 787; b) W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574; c) G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, H. Cheng, *J. Org. Chem.* **1999**, *64*, 7048.

[5] S. C. Sondej, J. A. Katzenellenbogen, *J. Org. Chem.* **1986**, *51*, 3508.

[6] K. Matsuda, J. A. Sedlak, J. S. Noland, G. C. Gleckler, *J. Org. Chem.* **1962**, *27*, 4015.

[7] Recently, milder conditions for the hydrofluorination of alkynes have been reported. For example, a) O. E. Okoromoba, J. Han, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2014**, *136*, 14381; b) Z. Lu, B. S. Bajwa, S. Liu, S. Lee, G. B. Hammond, B. Xu, *Green Chem.* **2019**, *21*, 1467.

[8] Z. Feng, Y.-L. Xiao, X. Zhang, *Acc. Chem. Res.* **2018**, *51*, 2264.

[9] Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo, X. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 1230.

[10] L. Tang, Z.-Y. Liu, W. She, C. Feng, *Chem. Sci.* **2019**, *10*, 8701.

[11] 3-Bromo-3,3-difluoropropene is available from SynQuest Laboratories, Inc. for \$ 895/25 g, \$ 5619 mol^{-1}.

[12] a) P. Tarrant, M. Lovelace, *J. Am. Chem. Soc.* **1954**, *76*, 3466; b) D. Seyferth, R. M. Simon, D. J. Sepelak, H. A. Klein, *J. Org. Chem.* **1980**, *45*, 2273.

[13] D. C. Blakemore, P. M. Doyle, Y. M. Fobian, *Synthetic Methods in Drug Discovery*, 1st ed., RSC Publishing, **2015**.

[14] 3,3,3-Trifluoropropene is available from SynQuest Laboratories, Inc. for \$ 450/500 g, \$ 86 mol^{-1}.

[15] Y.-G. Lou, A.-J. Wang, L. Zhao, L.-F. He, X.-F. Li, C.-Y. He, X. Zhang, *Chem. Commun.* **2019**, *55*, 3705.

[16] P. C. Ramachandran, A. Tafelska-Kaczmarek, A. Chatterjee, *J. Org. Chem.* **2012**, *77*, 9329.

[17] Defluorinative borylation of trifluoromethyl-substituted alkenes: a) R. Corberán, N. W. Mszar, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2011**, *50*, 7079; *Angew. Chem.* **2011**, *123*, 7217; b) Y. Liu, Y. Zhou, Y. Zhao, J. Qu, *Org. Lett.* **2017**, *19*, 946; c) R. Kojima, S. Akiyama, H. Ito, *Angew. Chem. Int. Ed.* **2018**, *57*, 7196; *Angew. Chem.* **2018**, *130*, 7314; d) P. Gao, C. Yuan, Y. Zhao, Z. Shi, *Chem* **2018**, *4*, 2201; e) X. Zhao, C. Li, B. Wang, S. Cao, *Tetrahedron Lett.* **2019**, *60*, 129; f) P. H. S. Paioti, J. del Pozo, M. S. Mikus, J. Lee, M. J. Koh, F. Romiti, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 19917; g) Y. Liu, C. Li, C. Liu, J. He, X. Zhao, S. Cao, *Tetrahedron Lett.* **2020**, *61*, 151940.

[18] Defluorinative borylation of difluoromethyl-substituted alkenes: a) S. Akiyama, K. Kubota, M. S. Mikus, P. H. S. Paioti, F. Romiti, Q. Liu, Y. Zhou, A. H. Hoveyda, H. Ito, *Angew. Chem. Int. Ed.* **2019**, *58*, 11998; *Angew. Chem.* **2019**, *131*, 12126; b) T. W. Butcher, J. L. Yang, J. F. Hartwig, *Org. Lett.* **2020**, *22*, 6805.
[19] For example, a) S. Kotha, M. Behera, V. R. Shah, *Synlett* **2005**, 1877; b) D. C. Gerbino, S. D. Mandolesi, H.-G. Schmalz, J. C. Podest, *Eur. J. Org. Chem.* **2009**, 3964; c) S. Kotha, A. S. Chavan, M. Shaikh, *J. Org. Chem.* **2012**, *77*, 482.
[20] Y. Ohtsuka, O. Kobayashi, T. Yamakawa, *J. Fluorine Chem.* **2014**, *161*, 34.
[21] W. Chen, L. Xu, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 4275.
[22] Palladium-catalyzed defluorinative substitution of difluoroallyl compounds via π-allyl complex: a) X. Pigeon, M. Bergeron, F. Barabé, P. Dubé, H. N. Frost, J.-F. Paquin, *Angew. Chem. Int. Ed.* **2010**, *49*, 1123; *Angew. Chem.* **2010**, *122*, 1141; b) M. Drouin, S. Tremblay, J.-F. Paquin, *Org. Biomol. Chem.* **2017**, *15*, 2376.
[23] For example, T. Powers, C. Steeneck, R. Biesinger, H. Bluhm, H. Deng, R. Dodd, B. M. J. Gallagher, C. Gege, M. Hochgurtel, A. Kiely, F. Richter, M. Schneider, I. Sucholeiki, V. J. Van, X. Wu, A. G. Taveras, WO2006083454, **2006**.
[24] T. W. Butcher, J. L. Yang, W. M. Amberg, N. B. Watkins, N. D. Wilkinson, J. F. Hartwig, *Nature* **2020**, *583*, 548.

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