Difluoroalkylation

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Synthesis of α,α-Difluoromethylene Alkynes by Palladium-Catalyzed *gem*-Difluoropropargylation of Aryl and Alkenyl Boron Reagents**

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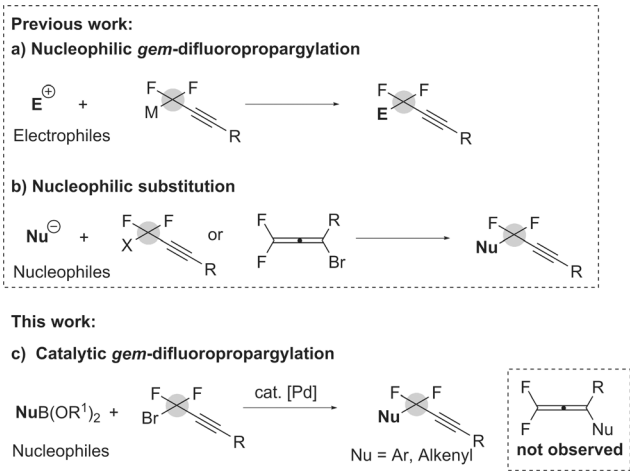
Abstract: *gem-Difluoropropargyl bromides are versatile intermediates in organic synthesis, but have rarely been employed in transition-metal-catalyzed cross-coupling reactions. The first palladium-catalyzed gem-difluoropropargylation of organoboron reagents with gem-difluoropropargyl bromides is now reported. The reaction proceeds under mild reaction conditions with high regioselectivity; it features a broad substrate scope and excellent functional-group compatibility and thus provides an attractive approach for the synthesis of complex fluorinated molecules, in particular for drug discovery and development.*

Alkynes are of paramount importance in organic chemistry.[1] Conceptually, the replacement of a methylene group (CH_2) by its difluorinated counterpart (CF_2) at a propargylic position could lead to the discovery of novel reactions and the development of interesting molecules with applications in the life and material sciences because of the unique properties of the difluoromethylene group (CF_2), which often brings about profound changes in the physical, chemical, and biological properties of organic molecules.[2] In fact, α,α-difluoromethylene alkynes have become increasingly important for the synthesis of various fluorine-containing molecules[3] and in click chemistry.[4] Various methods have been developed for the synthesis of such *gem*-difluoropropargylated molecules, including direct *gem*-difluoropropargylation[5] and indirect transformations.[6] Although the direct approach is more attractive, most of the reported examples are limited to the nucleophilic *gem*-difluoropropargylation of electrophiles, such as aldehydes and imines (Scheme 1a).[5] There are rare examples for the synthesis of R−C≡C−CF_2Nu moieties through nucleophilic substitution on a CF_2 group,[7] and only one example using carbon-centered nucleophiles (alkynyl lithium reagents) with limited substrate scope was reported,[7a] probably because of the electronic repulsion between the fluorine atoms and the incoming nucleophile. In this context, an alternative strategy was recently reported, in which the R−C≡C−CF_2Nu moiety was prepared through an S_N2' reaction between γ-bromodifluoroallenes and different nucleophiles (Scheme 1b).[8] This opened up a new way for the preparation of such valuable fluorinated molecules. However, γ-bromodifluoroallene is unstable at room temperature, and additional steps are required for its preparation. Furthermore, the intrinsic limitations of these nucleophilic substitution reactions, such as a requirement for strong nucleophiles and their incompatibility with base- or nucleophile-sensitive functional groups, restrict their wide application in organic synthesis. In terms of synthetic simplicity and generality, it is highly desirable to develop new strategies and efficient methods to access compounds with a R−C≡C−CF_2Nu moiety. In continuation of our interest in transition-metal-catalyzed fluoroalkylation reactions,[9] we herein describe the first palladium-catalyzed *gem*-difluoropropargylation of organoboron species, which proceeds with high efficiency (Scheme 1c). This process is applicable to a range of *gem*-difluoropropargyl bromides and organoboron species, including aryl and alkenyl boronic acids and boronates. The mild reaction conditions enable the formation of C−CF_2R bonds with excellent functional-group compatibility, even a benzyl bromide moiety was tolerated. Notably, only propargylic products were obtained with our catalytic system. This is in sharp contrast to previous reports, where palladium-catalyzed cross-coupling reactions of propargylic halides or alcohols with organoboronic acids often led to mixtures of allenic and propargylic products.[10]



Scheme 1. Strategies for direct *gem*-difluoropropargylation.

We began our studies by choosing air-stable phenylboronic acid (**1a**) and *gem*-difluoropropargyl bromide **2a** as model substrates to identify an active Pd catalyst and suitable reaction parameters to conduct this transformation under mild conditions. **2a** can be easily prepared from the reaction

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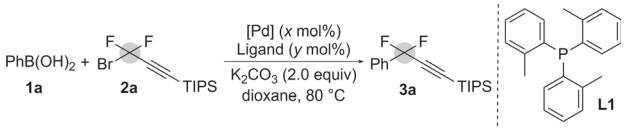
Table 1: Optimization of the Pd-catalyzed *gem*-difluoropropargylation of phenyl boronic acid (**1a**) with *gem*-difluoropropargyl bromide **2a**.[a]



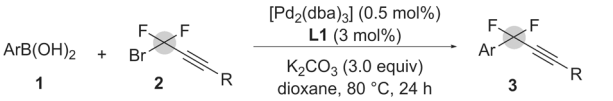
Entry	[Pd] (mol%)	Ligand (mol%)	*t* [h]	Yield[b] [%]
1	$[Pd_2(dba)_3]$ (2.5)	–	12	nd
2	$[Pd_2(dba)_3]$ (2.5)	PPh_3 (10)	12	8
3	$[Pd_2(dba)_3]$ (2.5)	MePhos (10)	12	3
4	$[Pd_2(dba)_3]$ (2.5)	CyJohnPhos (10)	12	9
5	$[Pd_2(dba)_3]$ (2.5)	$P(tBu)_3 \cdot HBF_4$ (10)	12	19
6	$[Pd_2(dba)_3]$ (2.5)	**L1** (10)	12	62
7	$[Pd_2(dba)_3]$ (2.5)	**L2** (10)	12	29
8	$[Pd_2(dba)_3]$ (2.5)	XantPhos (5)	12	9
9	$[Pd_2(dba)_3]$ (2.5)	**L1** (5)	12	53
10	$[Pd_2(dba)_3]$ (2.5)	**L1** (15)	12	85
11	$[Pd_2(dba)_3]$ (2.5)	**L1** (20)	12	42
12	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	**L1** (15)	12	73
13	$[Pd(PPh_3)_4]$ (5)	**L1** (15)	12	10
14	$Pd(OAc)_2$ (5)	**L1** (15)	12	39
15	$Pd(TFA)_2$ (5)	**L1** (15)	12	70
16	$[Pd_2(dba)_3]$ (2.5)	**L1** (15)	24	96
17	$[Pd_2(dba)_3]$ (1.25)	**L1** (7.5)	24	97
18[c]	$[Pd_2(dba)_3]$ (0.5)	**L1** (3)	24	93 (91)

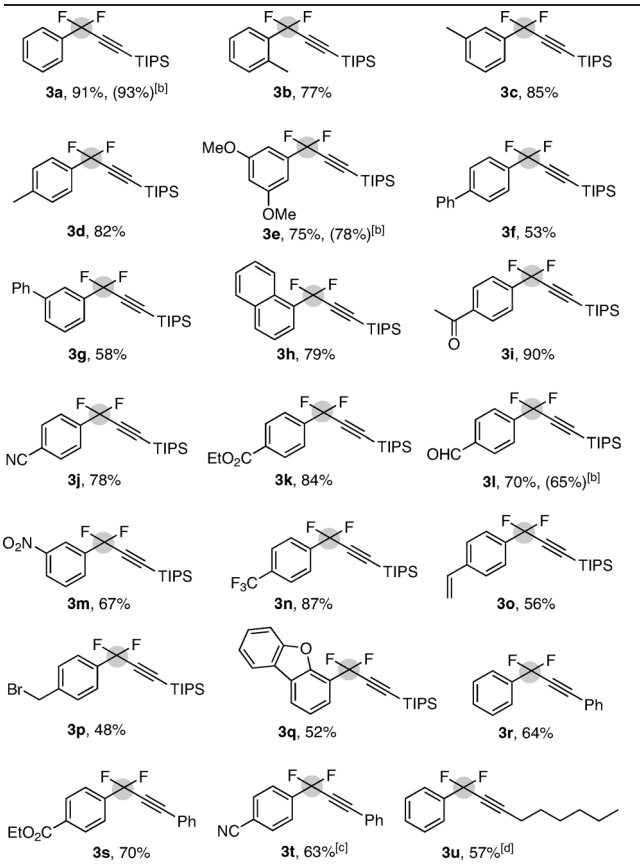
[a] Reaction conditions (unless otherwise specified): **1a** (1.2 equiv), **2a** (0.3 mmol, 1.0 equiv), K_2CO_3 (2.0 equiv), dioxane (2 mL), 80°C. [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard; the value in brackets denotes the yield of isolated product. [c] K_2CO_3 (3.0 equiv). dba = (*E*,*E*)-dibenzylideneacetone, CyJohnPhos = (2-biphenyl)dicyclohexylphosphine, **L2** = tris(2-methoxyphenyl)phosphine, MePhos = 2-methyl-2′-dicyclohexylphosphinobiphenyl, nd = not determined, TFA = trifluoroacetate, TIPS = triisopropylsilyl, XantPhos = 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene.

of ((triisopropylsilyl)ethynyl)lithium with CF_2Br_2[7a,11] (Table 1). Initially, the reaction was conducted with $[Pd_2(dba)_3]$ (5 mol%) and a range of phosphines in the presence of K_2CO_3 (2.0 equiv) in dioxane at 80°C (Table 1, entries 1–8). The reaction catalyzed by a combination of $[Pd_2(dba)_3]$ (5 mol%) and P(*o*-Tol)$_3$ (**L1**; 10 mol%) afforded the coupled product **3a** in 62% yield (determined by ^{19}F NMR spectroscopy), without formation of the allenic side product (entry 6). However, other ligands were inferior to **L1**; even the bisphosphine ligand XantPhos, which was previously demonstrated to be a suitable ligand for reductive elimination from fluoroalkyl palladium complexes,[12] afforded **3a** in only 9% yield (entry 8). We assume that this is due to the resistance of the bulky ligand **L1** to undergo quaternization and generate an active palladium catalyst $[Pd\{P(o\text{-Tol})_3\}_2]$, which benefits the oxidative addition of the RCF_2–Br bond to $[Pd\{P(o\text{-Tol})_3\}_2]$.[13] With regard to the existence of an equilibrium between $[\{(o\text{-Tol})_3P\}_nPd(dba)_m]$ and $[Pd\{P(o\text{-Tol})_3\}_2]$,[13c] the $[Pd_2(dba)_3]$/**L1** ratio was examined to further improve the reaction efficiency (entries 9–11). **3a** was obtained in a substantially improved yield (85%) with a Pd/**L1** ratio of 1:3 (entry 10). Encouraged by these results, different Pd catalysts were investigated (entries 12–15). We found that the reaction was sensitive to the nature of the Pd catalyst. $[Pd_2(dba)_3]$ was the best choice. The use of $[Pd_2(dba)_3]\cdot CHCl_3$ led to a diminished yield (entry 12), and a poor yield (10%) of **3a** was obtained when employing $[Pd(PPh_3)_4]$ as the catalyst (entry 13), demonstrating that the ligand exchange between PPh_3 and **L1** is difficult because of the lability of **L1**.[13] Finally, the optimized reaction conditions were identified by decreasing the amount of $[Pd_2(dba)_3]$ to 0.5 mol% and entailed the use of **L1** (3 mol%) and K_2CO_3 (3.0 equiv) in dioxane at 80°C for 24 hours; **3a** was thus isolated in 91% yield (entry 18; for details, see the Supporting Information).

Upon the identification of viable reaction conditions, a wide range of aryl boronic acids were employed as substrates in this transformation (Table 2). In general, aryl boronic acids with electronically different substituents underwent the present cross-coupling process with *gem*-difluoropropargyl bromide **2a** in moderate to high yields. Notably, even when the amount of $[Pd_2(dba)_3]$ was decreased to

Table 2: Palladium-catalyzed *gem*-difluoropropargylation of aryl boronic acids **1** with *gem*-difluoropropargyl bromides **2**.[a]





[a] Reaction conditions (unless otherwise specified): **1** (1.2 equiv), **2** (0.6 mmol, 1.0 equiv), dioxane (3 mL). Yields of isolated products are given. [b] $[Pd_2(dba)_3]$ (0.1 mol%) and **L1** (0.6 mol%). [c] $[Pd_2(dba)_3]$ (1.25 mol%) and **L1** (7.5 mol%) at 100°C. [d] $[Pd_2(dba)_3]$ (2.5 mol%) and **L1** (15 mol%) in toluene.

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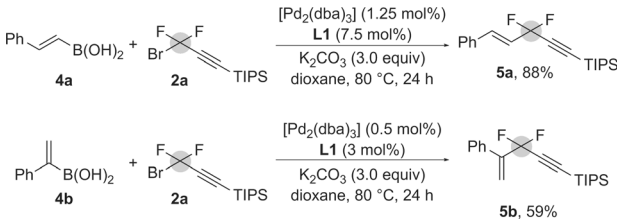
0.1 mol%, **3a**, **3e**, and **3l** were still obtained in high yields. A variety of versatile functional groups, including base- or nucleophile-sensitive moieties, such as enolizable ketone, cyano, alkoxycarbonyl, formyl, nitro, and alkenyl groups, were tolerated quite well (**3i–m** and **3o**). 4-(Bromomethyl)-phenyl)boronic acid (**1p**) only furnished the corresponding product **3p** in moderate yield because of the formation of some unidentifiable side products from **1p**. A dibenzo-[*b*,*d*]furan-derived aryl boronic acid was also a suitable coupling partner (**3q**). Moreover, sterically hindered *ortho*-tolylboronic acid and naphthalen-1-ylboronic acid were excellent substrates, and the cross-couplings with **2a** proceeded with high efficiency (**3b** and **3h**). The reaction was not restricted to *gem*-difluoropropargyl bromide **2a**, as aromatic and aliphatic *gem*-difluoropropargyl bromides were also suitable and provided the corresponding products in good yields (**3r–u**). Only propargylic fluorinated products were produced from these substrates. This is in sharp contrast to the reactions of their non-fluorinated counterparts, where a mixture of allenic and propargylic products is often obtained.[10]

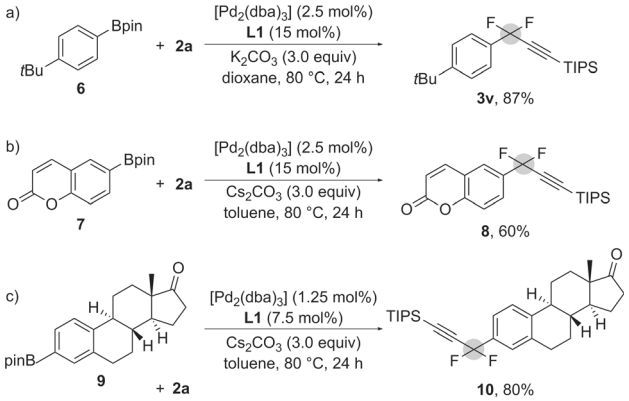
The reaction can also be extended to alkenyl boronic acids. Linear and branched alkenyl boronic acids underwent the reaction with *gem*-difluoropropargyl bromide **2a** in moderate to high yields (Scheme 2). The rather lower yield of **5b** is probably due to steric effects. In light of the



Scheme 2. Palladium-catalyzed *gem*-difluoropropargylation of alkenyl boronic acids with *gem*-difluoropropargyl bromide **2a**.

importance of the enyne motif in organic synthesis,[14] this transformation is highly relevant for the synthesis of complex fluorinated molecules. However, previous methods to access such structural motifs relied on stepwise procedures that required the preparation of acetylenic ketones and subsequent deoxygenative fluorination,[6] which highlights the synthetic simplicity and efficacy of the present method.

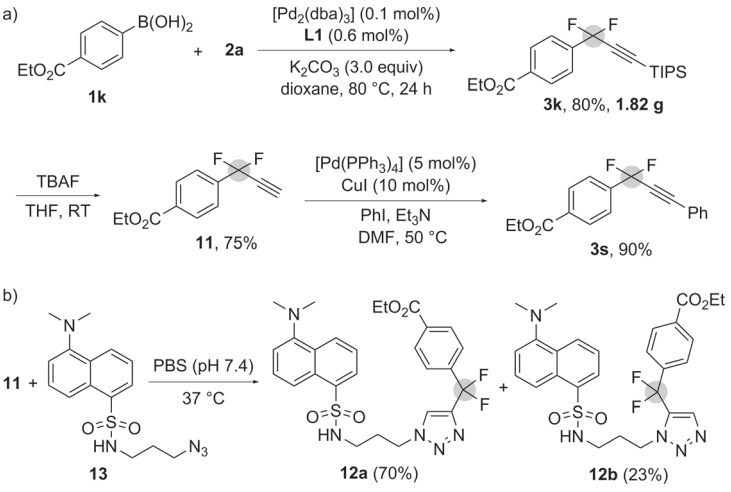
The reaction of *gem*-difluoropropargyl bromide with aryl boronates is also feasible (Scheme 3). **3v** was obtained in high yield when aryl boronate **6** was treated with **2a** in the presence of $[Pd_2(dba)_3]$ (2.5 mol%) and **L1** (15 mol%; Scheme 3a). To highlight the utility of this method for the late-stage difluoroalkylation of biologically active molecules, the *gem*-difluoropropargylation of coumarin-derived aryl boronate **7** was conducted, which delivered compound **8** in 60% yield without affecting the α,β-unsaturated lactone. This is noteworthy as coumarin and its derivatives exhibit significant biological activities,



Scheme 3. Late-stage difluoropropargylation of biologically active molecules. pin = pinacolato.

such as anti-HIV, anti-tumor, and antihypertensive properties.[15] Therefore, this method is a valuable strategy for coumarin modification and for the discovery of new interesting molecules (Scheme 3b). The importance of this process was also exemplified by the efficient synthesis of *gem*-difluoropropargylated estrone **10** from aryl boronate **9** (Scheme 3c). Considering the facile access to aromatic pinacol esters through iridium-catalyzed C–H borylation,[16] we view this as a particularly attractive approach for the late-stage fluorination of biologically active molecules for drug discovery and development.

To further demonstrate the utility of this method, transformations of the resulting difluoropropargylated arenes were also investigated. As illustrated in Scheme 4a, the gram-scale synthesis of **3k** proceeded with high efficiency (80% yield) even when using only 0.1 mol% of $[Pd_2(dba)_3]$, thus highlighting the reliability of this process. Subsequently, deprotection of **3k** with TBAF, followed by a Sonogashira reaction, afforded compound **3s** in high yield. On the basis of this strategy, a series of carbon-substituted internal alkynes with a CF_2Ar substituent could be efficiently prepared, offering a complementary method to the approach illustrated in



Scheme 4. Transformations of alkyne **3k**. TBAF = tetrabutylammonium fluoride.

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Table 2 (**3r–u**). Although the copper-catalyzed click reaction between azides and terminal alkynes has many applications,[17] copper-free click reactions remain appealing because of the cytotoxicity of copper(I) species.[17a] To our delight, the [3+2] cycloaddition product **12** was obtained in high yield (93%, as a mixture of regioisomers: **12a**, 70%; **12b**, 23%) when terminal alkyne **11** was treated with the dansyl fluorophore **13** in the absence of copper in phosphate buffered saline (PBS; pH 7.4) at 37°C. Yet, only a poor yield (6%) was obtained when the non-fluorinated terminal alkyne was used under the same reaction conditions (for details, see the Supporting Information), which demonstrates that the presence of the CF_2 moiety was essential for the high reactivity of the substrate in the click reaction. This is because the CF_2 moiety not only lowers the LUMO of the difluoroalkylated alkyne,[18] but also increases the stability of the transition state (TS) through hyperconjugative interactions between the alkyne π system and vicinal σ^*_{C-F} acceptors.[19] In view of its good reactivity, simple synthesis, and stability, we believe that terminal alkyne **11** and its derivatives may have applications in drug development and chemical biology.

To probe whether a difluoroalkyl radical existed in the reaction, radical inhibition experiments were conducted (for details, see the Supporting Information). No substantially decreased yields of **3a** were observed when a radical initiator [azobisisobutyronitrile (AIBN)], radical inhibitors [hydroquinone or butylated hydroxytoluene (BHT)], or an electron transfer (ET) inhibitor (1,4-dinitrobenzene) were added to the reaction of **1a** with **2a** in the presence of $[Pd_2(dba)_3]$ (0.5 mol%), **L1** (3 mol%), and K_2CO_3 in dioxane.[20] On the basis of these preliminary studies, a pathway that involves a free *gem*-difluoropropargyl radical is less likely. However, a radical mechanism cannot be excluded. We propose that the oxidative addition of RCF_2–Br to the $[Pd^0L_n]$ species to generate a mixture of propargylic palladium complex **I** and allenylpalladium complex **II** is the initial step, in which intermediate **II** may equilibrate with intermediate **I**.[21] Under the present reaction conditions (80°C), the less thermally stable species **II** would be converted into the thermally stable species **I**. This species would subsequently undergo transmetalation to give aryl palladium *gem*-difluoropropargyl intermediate $[ArPd(L)_nCF_2C{\equiv}CR]$ (**III**), followed by reductive elimination to give the final products.

In conclusion, we have reported the first palladium-catalyzed *gem*-difluoropropargylation of organoboron compounds with *gem*-difluoropropargyl bromides. The simple P(*o*-Tol)$_3$ ligand is critical for the reaction efficiency, whereas in previous reports, phosphine ligands with large bite angles[12] or extremely bulky substituents[22] were required for reductive elimination from the aryl palladium fluoroalkyl complexes. Most of these target molecules were previously unknown and should become versatile and important building blocks to be used in organic synthesis and medicinal chemistry. The notable features of this method are its high regioselectivity, broad substrate scope, and excellent functional-group compatibility. The successful late-stage difluoroalkylation of bioactive compounds and the copper-free click reaction of a difluoroalkylated terminal alkyne provide good opportunities for applications in drug discovery and development. Further studies to develop derivative reactions are underway in our laboratory and will be reported in due course.

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