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Palladium-Catalyzed Anti-Markovnikov Hydroalkylation of Homoallylic Alcohols Bearing β-Fluorines

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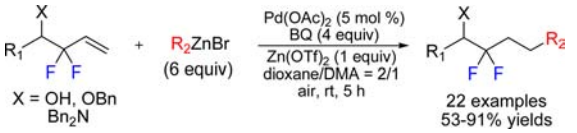
ABSTRACT



A palladium-catalyzed anti-Markovnikov hydroalkylation of β,β-difluorinated homoallylic alcohols with alkylzinc reagents has been developed. This method affords a wide range of synthetically useful *gem*-difluorinated compounds with good functional group compatibility.

Transition-metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents are widely used for carbon−carbon formation.[1] Historically, development of the efficient cross-coupling of alkyl halides or pseudohalides with alkyl organometallics to form the $C(sp^3)-C(sp^3)$ bonds has been much slower than the related $C(sp^2)-C(sp^2)$ coupling. This was probably due to the slow oxidative addition of alkyl electrophiles with low-valent metal complexes, and the resultant alkyl−metal complexes may suffer from competitive side reactions (β-hydride elimination, hydrodehalogenation). In the past four decades, since the pioneering works by Kochi and Tamura,[2] Suzuki et al.,[3] and Knochel et al.,[4] many efficient cross-coupling catalyst systems have been developed for the $C(sp^3)-C(sp^3)$ bond formation.[5] Very recently, Sigman and co-workers have reported an alternative substrate control tactic to formally construct a new $C(sp^3)-C(sp^3)$ bond using alkenes, including styrenes,[6] allylic amines,[7] allylic alcohols, and homoallylic alcohols,[8] as surrogates for alkyl electrophiles. However, the substitution at the allylic position of homoallylic alcohols was essential for the formation of the anti-Markovnikov product in high yield and selectivity (Scheme 1a). For example, a protected homoallylic alcohol, lacking substitution at the allylic position, was used as a coupling partner to afford a 2.8:1 mixture of anti-Markovnikov (**I**) and Markovnikov (**II**) products in low yield (< 20%) (Scheme 1b).[8]

The extreme electronegativity of the fluorine atom results in the electron-withdrawing character of a

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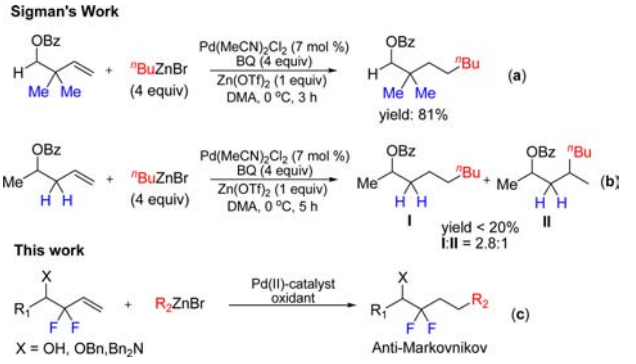
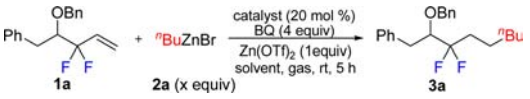
Scheme 1. Hydroalkylation of Homoallylic Alcohols and β,β-Difluorinated Homoallylic Alcohols



gem-difluoromethylene group (CF_2).[9] The incorporation of a CF_2 group into organic molecules has a profound influence on their chemical and physical properties.[10] Therefore, the transposition of CH_2 to CF_2 at the allylic position of the homoallylic alcohol can modify the electronic and steric environment of the alkene of interest. Recently, the efforts of our group have focused on the development of the carbon−carbon bond formation by using *gem*-difluorinated compounds as coupling partners.[11] Herein, we report the palladium-catalyzed cross-coupling reactions of β,β-difluorinated homoallylic alcohols with alkylzinc reagents to afford the anti-Markovnikov *gem*-difluoromethylene-containing hydroalkylated products in high yields (Scheme 1c).

We initiated our studies by testing the reactions of (2-(benzyloxy)-3,3-difluoropent-4-enyl)benzene **1a** and ^{n}BuZnBr **2a** catalyzed by palladium complexes (Table 1). Sigman and co-workers[6−8] reported that Pd(I^{i}Pr)(OTs)$_2$ and $Pd(MeCN)_2Cl_2$ showed excellent activities for the anti-Markovnikov hydroalkylation of organozinc reagents with alkenes. Unfortunately, when we attempted the coupling reactions of **1a** and **2a** using Pd(I^{i}Pr)(OTs)$_2$ and $Pd(MeCN)_2Cl_2$ as catalysts and benzoquinnone (BQ) as oxidant, only a small amount of hydroalkylation product **3a** was detected (entries 1, 2). When $Pd(OAc)_2$ was employed as catalyst, a 23% yield of **3a** was obtained (entry 3). It has been reported that O_2 can be used as a terminal oxidant.[12] Therefore, the reaction of **1a** and **2a** was carried out under aerobic oxidation conditions. However, no desired product was observed, and the starting material **1a** was recovered completely (entry 4).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	x	gas[b]	solvent	yield of **3a** (%)[c]
1	Pd(I^{i}Pr)(OTs)$_2$	4	Ar	DMA	8
2	$Pd(MeCN)_2Cl_2$	4	Ar	DMA	5
3	$Pd(OAc)_2$	4	Ar	DMA	23
4[d]	$Pd(OAc)_2$	0	O_2	DMA	0[e]
5	$Pd(OAc)_2$	4	O_2	DMA	37
6	$Pd(OAc)_2$	4	air	DMA	39
7	$Pd(OAc)_2$	6	air	DMA	50
8	$Pd(OAc)_2$	8	air	DMA	48
9	$Pd(OAc)_2$	6	air	DMF	31
10	$Pd(OAc)_2$	6	air	DCM	51
11	$Pd(OAc)_2$	6	air	THF	52
12	$Pd(OAc)_2$	6	air	dioxane	60
13	$Pd(OAc)_2$	6	air	xylene	29
14[f]	$Pd(OAc)_2$	6	air	dioxane	75
15[g]	$Pd(OAc)_2$	6	air	dioxane	63
16[f,h]	$Pd(OAc)_2$	6	air	dioxane	78
17[f]		6	air	dioxane	0[e]

[a] Reactions were carried out on a 0.2 mmol scale. Unless stated otherwise, ^{n}BuZnBr was added dropwise to the reaction mixture within 10 min. BQ = benzoquinone. [b] Gas balloon was used. [c] Yield relative to benzotrifluoride as an internal standard was determined by ^{19}F NMR. [d] Without BQ. [e] **1a** was recovered completely. [f] ^{n}BuZnBr was added dropwise to the reaction mixture over 45 min. [g] ^{n}BuZnBr was added dropwise to the reaction mixture over 60 min. [h] 5 mol % of $Pd(OAc)_2$ was used.

Surprisingly, when benzoquinone (BQ) was used as oxidant with O_2 as co-oxidant, a 37% yield of the hydroalkylation product was formed (entry 5). It indicated that BQ is essential to this reaction. Recently, Lei and co-workers[13] described that dry air can also be used as the terminal oxidant for the Pd-catalyzed aerobic oxidative cross-coupling between terminal alkynes and alkylzinc reagents. Accordingly, when **1a** and **2a** were treated with BQ under a dry air atmosphere, the yield of **3a** was slightly improved to 39% (entry 6). In consideration of the fact that ^{n}BuZnBr **2a** served not only as a coupling partner but also as a hydride source, the increasing amount of ^{n}BuZnBr **2a** would result in better performance of the coupling reaction. As expected, the desired product **3a** was formed in 50% yield in the presence of 6 equiv of ^{n}BuZnBr **2a** (entry 7). However, when the amount of ^{n}BuZnBr **2a** was further increased, there was no improvement of this reaction (entry 8). The exploration of solvents then demonstrated that dioxane was the most efficient solvent (entries 9−13). To our delight, when ^{n}BuZnBr **2a** was added dropwise to the reaction mixture over 45 min, the yield of **3a** was further improved to 75% yield (entry 14). Nevertheless, the addition of ^{n}BuZnBr **2a** to the reaction mixture over 60 min led to the lower yield of **3a** (entry 15). Interestingly, the reaction of **1a** and **2a**

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proceeded smoothly and provided a slightly higher yield of **3a** when the amount of $Pd(OAc)_2$ was decreaed from 20 to 5 mol % (entry 16). No product formation was observed without palladium catalyst (entry 17).

With the optimized conditions in hand (Table 1, entry 16), the substrate scope (β,β-difluorinated homoallylic alcohols and alkylzinc reagents) of the hydroalkylation reaction was investigated. As shown in Table 2, benzyl-protected β,β-difluorinated homoallylic alcohol **1a** reacted with ^{n}BuZnBr **2a** smoothly to give the linear hydroalkylation product **3a** in 78% yield (entry 1). A free homoallylic alcohol **1a′** also gave the coupling product **3a′** in 73% yield (entry 2). Additionally, the homoallylic alcohols bearing an alkyl-substitution on R^1 underwent efficient hydroalkylation with **2a** to give the coupling products (**3b′**, **3c**, **3c′**) in good yields (entries 3−5). The doubly protected homoallylic amine **1e** was found to be compatible with the reaction conditions, furnishing compound **3e** in 59% yield (entry 8). In addition, substrates with electron-donating (**1f**−**1g′**) or electron-withdrawing (**1h**−**1i′**) substituents as well as *ortho* substituents (**1g**, **1g′**) on the arene were efficient coupling partners to afford the coupled products in moderate to good yields (entries 9−17). In comparison, the products (**3f**−**3g′**) with electron-donating groups were obtained in slightly higher yields than the products (**3h**−**3i′**) with electron-withdrawing groups. It was noteworthy that aryl chloride (**3j**, **3j′**) could be retained; no product arising from the Negishi-type coupling was observed, providing opportunities for further transformation. Further investigation revealed that a heteroaromatic thiophene group was also well tolerated to give the product (**3k**, **3k′**) in good yields (entries 18, 19). Interestingly, when the substrate (**1l′**) containing both internal and terminal double bonds was subjected to the coupling reaction conditions, the linear product (**3l′**) was formed exclusively in 73% yield, in which the internal double bond remained intact (entry 20). Finally, our attention was turned to the compatibility of alkyl organozinc reagents. It was found that the hydroalkylation of **1f** with octylzinc(II) bromide and (cyclohexylmethyl)zinc(II) bromide gave the products **3m** and **3n**, respectively, in good yields (entries 21, 22). It should be noted that the anti-Markonikov product (linear product) was exclusively formed in the palladium-catalyzed hydroalkylation of β,β-difluorinated homoallylic alcohol derivatives with alkylzinc reagents (Tables 1 and 2).

To illustrate the synthetic application of this palladium-catalyzed hydroalkylation reaction, we undertook the preparation of **10** (Scheme 2). Compound **10** is an important precursor in the synthesis of target molecular 4-deoxy-4,4-difluoro-KRN7000,[14] which is a potent stimulator of Natural Killer T-cells (NKT-cells). The preparation of **10**

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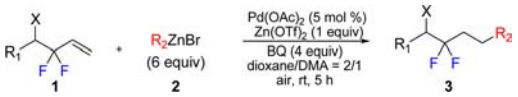
Table 2. Substrate Scope of the Pd-Catalyzed Hydroalkylation[a,b,c]

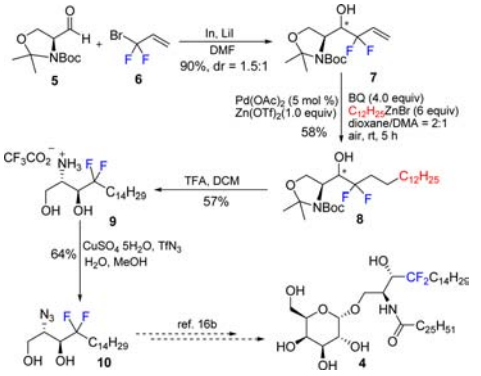


entry	substrate **1**	product **3**	yield (%)
1			78
2			73
3			72
4			64
5			53
6			81
7			71
8			59
9			91
10			77
11			84
12			71
13			67
14			60
15			62
16			70
17			66
18			81
19			70
20			73
21[b]			84
22[c]			67

[a] Unless stated otherwise, reactions were performed using **1** (0.4 mmol), *n*BuZnBr (6 equiv), $Pd(OAc)_2$ (5 mol %), BQ (4 equiv), and $Zn(OTf)_2$ (1 equiv) in dioxane/DMA at room temperature for 5 h under a dry air atomosphere. Isolated yield. [b] $C_8H_{17}ZnBr$ was used. [c] $CyCH_2ZnBr$ was used.

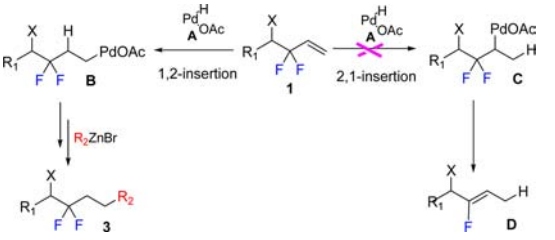
started from commercially available Garner's aldehyde **5** (Scheme 2). The allylation of aldehyde **5** with 3-bromo-3,3-difluoroprop-1-ene **6** provided the β,β-difluorinated homoallylic alcohol **7** in 90% yield (dr = 1.5:1). The two diastereomers of **7** could not be separated by chromatography. Treatment of alcohol **7** with dodecylzinc(II) bromide under the optimized Pd-catalyzed hydroalkylation reaction conditions provided the linear product **8** in 58% yield. Subsequently, deprotection of compound **8** gave the ammonium salt **9** in 57% yield. Finally, the transformation of the amino group of compound **9** to the azide group gave the important precursor **10** in 64% yield.

Scheme 2. Synthesis of the Precursor of 4-Deoxy-4,4-difluoro-KRN7000



On the basis of Sigman's works on palladium-catalyzed hydroalkylation of olefins with organozinc reagents,[6−8] we proposed the reaction mechanism outlined in Scheme 3. The transmetalation of the Pd(II) complex with organozinc reagent **2**, followed by β-hydride elimination, gave Pd-hydride **A**. The coordination and insertion of **A** with β,β-difluorinated homoallylic alcohol derivative **1** would proceed via either a 1,2-insertion or a 2,1-insertion to give intermediates **B** and **C**, respectively. As the *gem*-difluoromethylene (CF_2) group is the electron-withdrawing group, the 1,2-insertion would proceed preferentially to give intermediate **B**. Further, in the case of a 2,1-insertion, the formed intermediate **C** would easily undergo β-fluoro elimination to afford compound **D**.[15] The ^{19}F NMR of the reaction mixture showed that compound **D** was not formed. Therefore, the insertion of Pd-hydride **A** to the double bond of difluorinated homoallylic alcohol derivative **1** proceeded exclusively via 1,2-insertion. Finally, the primary Pd−alkyl intermediate **B** underwent transmetalation, followed by reductive elimination, to give the anti-Markonikov product **3**.

Scheme 3. Proposed Mechanism



In summary, we have developed a complementary protocol for the synthesis of *gem*-difluorinated compounds through a palladium-catalyzed hydroalkylation of β,β-difluorinated homoallylic alcohols with alkyl organozinc reagents. This result further showed that the transposition of CH_2 to CF_2 at the allylic position of the homoallylic alcohols can modify the electronic and steric environment of alkenes, and the β,β-difluorinated homoallylic alcohols successfully afforded the anti-Markovnikov product selectively.

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Supporting Information Available. Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.