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γ-Selective Addition to 1,1-Difluoroallenes: Three-component Coupling Leading to 2,2-Disubstituted 1,1-Difluoroalkenes

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1,1-Difluoroallenes underwent γ-selective addition with alkylcopper reagents. The resulting 2,2-difluorovinylcopper intermediates were captured by electrophiles or subjected to palladium-catalyzed coupling to give 2,2-disubstituted 1,1-difluoroalkenes in good yield.

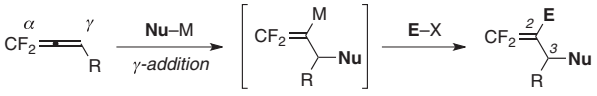
1,1-Difluoroalkenes are useful as synthetic intermediates and components of pharmaceuticals and agrochemicals. They incorporate an electrophilic and polarized double bond as well as vinylic fluorines with leaving group ability,[1] which leads them to react with nucleophiles rather than electrophiles at the vinylic CF_2 carbon to give monofluorinated alkenes (S_NV reaction).[2,3] The difluoroalkene moiety is also used for the development of potential mechanism-based enzyme inhibitors[4] and as a bioisostere for the carbonyl group, which leads to enhancement of the biological activities of the original molecules.[5] In spite of the importance of difluoroalkenes, methods for their synthesis, especially routes to 2,2-disubstituted 1,1-difluoroalkenes, are still limited.[6,7]

Recently, we reported synthetic methods for the preparation of 1,1-difluoroallenes, in which difluorovinylidenation of carbonyl groups were readily effected to provide easy access to these allene derivatives arrayed with a variety of substituents.[8] On the basis of these results, we planned a new route for the synthesis of disubstituted 1,1-difluoroalkenes (Scheme 1). Nucleophilic addition of an organometallic species (Nu–M) at the γ-position of 1,1-difluoroallenes would give 2,2-difluorovinylmetal intermediates. Capture of these intermediates by electrophiles (E–X) would provide the desired 2,2-disubstituted 1,1-difluoroalkenes bearing newly introduced substituents on the C2 (E) and C3 (Nu) positions. However, organometallic species normally attack the α-position of difluoroallenes to give the S_NV products, monofluoroallenes,[9] and no γ-selective addition of a carbanion equivalent to a 1,1-difluoroallene has been reported.[10]

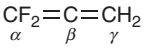
In order to examine the possibility of the nucleophilic addition at the γ-position, a DFT calculation was performed on 1,1-difluoroallene (Figure 1). The results suggested that 1,1-difluoroallene has a higher LUMO coefficient at the γ-carbon (0.693) than at the α-carbon (0.275), whereas a positive electrostatic charge is localized at the α-carbon (+0.272), and a negative charge is indicated at the γ-carbon (−0.341).[11] The desired γ-attack, therefore, might be accessible under orbital-controlled conditions.

Consequently, organometallic species were examined to study their potential for inducing γ-addition (Table 1). When difluoroallene **1** was treated with methyllithium or ethylmagnesium bromide, complex mixtures were obtained (Entries 1 and 2). Diethylzinc caused an undesired α-attack to form monofluoroallene **3a** in 12% yield (S_NV reaction, Entry 3). On the other hand, ethylcopper, generated in situ from ethylmagnesium bromide and the CuBr·SMe_2 complex, promoted the desired γ-addition to give difluoroalkene **2a** in 67% yield (Entry 4). However, a catalytic amount of CuBr·SMe_2 was not effective (Entry 5). Further optimization revealed that the use of CuBr and SMe_2 with ethyl- or butylmagnesium bromide gave the corresponding 3-alkyl-1,1-difluoroalkenes **2a** and **2b** in 95% and 93% yield, respectively (Entries 6 and 7). The γ-addition step probably generated difluorovinylcopper intermediates, and following a methanol quench, protonolysis gave the products **2**.[12]

Next, the 2,2-difluorovinylcopper intermediate was captured with electrophiles, which led to the corresponding functionalized 1,1-difluoroalkenes (Table 2). On treatment of the copper



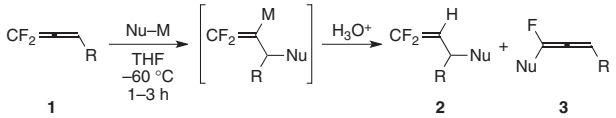
Scheme 1. Three-component coupling leading to 1,1-difluoroalkenes.



	C_α	C_β	C_γ
Coefficient of LUMO:	0.275	0.581	**0.693**
Electrostatic Charge:	**+0.272**	–0.067	–0.341

Figure 1. LUMO coefficients and electrostatic charges of 1,1-difluoroallene (B3LYP/6-31G*).

Table 1. γ-Selective addition to 1,1-difluoroallenes



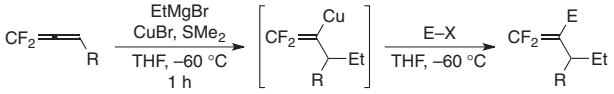
1 2 3

R = $(CH_2)_2$(1-Naph)

Entry	Nu–M (equiv)	**2**/%	**3**/%
1	MeLi (2.8)	—	—
2[a]	EtMgBr (2.8)	—	—
3[a]	Et_2Zn (1.7)	—	12, **3a**
4	EtMgBr (1.7), CuBr·SMe_2 (2.0)	67, **2a**	1, **3a**
5[a]	EtMgBr (1.0), CuBr·SMe_2 (0.1)	—	34, **3a**
6	EtMgBr (1.7) CuBr (1.7), SMe_2 (1.7)	95, **2a**	1, **3a**
7	*n*-BuMgBr (1.7) CuBr (1.7), SMe_2 (1.7)	93, **2b**	trace

[a]Difluoroallene **1** was recovered in 45% (Entry 2), 70% (Entry 3), and 53% yields (Entry 5), respectively.

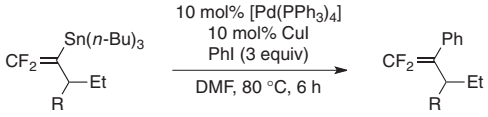
Table 2. Introduction of a halogen or stannyl group to difluoroallenes



1 R = $(CH_2)_2$(1-Naph) **2**

Entry	E–X (equiv)	E	*t*/h	**2**/%
1	NIS[a] (5.1)	I	2	84, **2c**
2	NBS[a] (1.7)	Br	2	75, **2d**
3	NCS[a] (5.1)	Cl	2	76, **2e**
4	*n*-Bu_3SnCl (1.7)	Sn(*n*-Bu)$_3$	3	66,[b] **2f**
5	Me_3SnCl (1.7)	$SnMe_3$	9	68,[b] **2g**

[a]NIS: *N*-iodosuccinimide, NBS: *N*-bromosuccinimide, NCS: *N*-chlorosuccinimide. [b] ^{19}F NMR yield ($PhCF_3$).



2f R = $(CH_2)_2$(1-Naph) **2h** 66% (^{19}F NMR yield, $PhCF_3$)

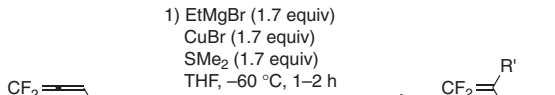
Scheme 2. Stille coupling of 2,2-difluorovinylstannane **2f**.

intermediate with NIS, NBS, or NCS, the corresponding 2-halogenated 1,1-difluoroalkenes **2c**–**2e** were obtained in 75%–84% yield (Entries 1–3). These 2-halo-1,1-difluoroalkenes act as efficient Suzuki coupling partners.[7g] Stannylation of the difluorovinylcopper species proceeded to give 2-tributylstannyl- and 2-trimethylstannyl-1,1-difluoroalkenes **2f** and **2g** in 66% and 68% yield, respectively (Entries 4 and 5). The obtained difluorovinylstannanes were then subjected to the Stille coupling reaction (Scheme 2).[7c,7e] Treatment of the isolated stannane **2f** with iodobenzene in the presence of $[Pd(PPh_3)_4]$ (10 mol %) and CuI (10 mol %) afforded the corresponding β,β-difluorostyrene **2h** in 66% yield.

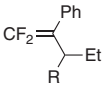
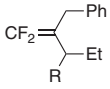
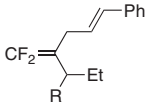
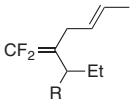
The above-mentioned γ-selective addition was combined with subsequent cross coupling in a one-pot operation to afford a three-component coupling (Table 3).[6,13–15] 1,1-Difluoroallene **1** was first subjected to the γ-selective addition of an ethylcopper reagent. When the resulting vinylcopper intermediates reacted with iodobenzene in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol % Pd) and PPh_3 (20 mol %), the desired difluorostyrene **2h** was obtained in 90% yield (Entry 1). A benzyl group was introduced by the one-pot coupling sequence to afford **2i** (Entry 2). Cinnamyl bromide and crotyl bromide were also advantageous, affording the corresponding 1,1-difluoroalka-1,4-dienes **2j** and **2k** in 66% and 85% yield, respectively, where allylation took place selectively at the α-carbon to the bromine substituent (Entries 3 and 4).

In summary, we developed a method for γ-selective addition to 1,1-difluoroallenes using organocopper reagents. The resulting difluorovinylcopper intermediates were captured by a wide range of electrophiles to give functionalized 1,1-difluoroalkenes that act as coupling partners. The γ-addition reaction was successfully followed by palladium-catalyzed cross

Table 3. Three-component synthesis of disubstituted 1,1-difluoroalkenes



1 R = $(CH_2)_2$(1-Naph) **2**

Entry	R′X	*t*/h	**2**	Yield/%
1	PhI	20		90, **2h**
2	$PhCH_2Br$	12		53,[a] **2i**
3	(*E*)-$PhCH_2$=$CHCH_2Br$	4		66,[b] **2j**
4	(*E*)-$MeCH_2$=$CHCH_2Br$	20		85,[b] **2k**

[a] ^{19}F NMR yield ($PhCF_3$). [b]Single regioisomer.

coupling to provide a three-component coupling sequence for the synthesis of 2,2-disubstituted 1,1-difluoroalkenes.

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11 For the graphical presentation of LUMO of 1,1-difluoroallene, see Supporting Information.[15]
12 Steric hindrance also plays an important role in the regioselectivity. Hammond and his co-workers reported that 3,3-disubstituted 1,1-difluoroallenes undergo α-attack under conditions identical to those used in this work to give **3**. See ref. 9b.
13 **Typical procedure**: To a THF (2 mL) suspension of copper(I) bromide (49 mg, 0.35 mmol) was added dimethyl sulfide (0.025 mL, 0.34 mmol) at room temperature, and the suspension was stirred for 2 h. A THF solution of ethylmagnesium bromide (0.90 mol L^{-1}, 0.38 mL, 0.34 mmol) was added to the suspension at −60 °C and stirred for 30 min at the same temperature. A hexane solution of 1,1-difluoroallene **1** (0.46 mol L^{-1}, 0.43 mL, 0.20 mmol) was added to the yellow suspension of ethylcopper reagent at −60 °C, and the mixture was stirred for 1 h. Hexamethylphosphoric triamide (0.50 mL), $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mg, 0.0097 mmol), and triphenylphosphine (11 mg, 0.042 mmol) were added, and the resulting solution was stirred for 15 min. After iodobenzene (0.022 mL, 0.20 mmol) was added, the reaction mixture was warmed to room temperature and stirred for 8 h. Phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (SiO_2, hexane) to give **2h** (60 mg, 90%) as a colorless liquid.[15]
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15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

