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Novel 2,2-Difluorovinylzirconocene: A Facile Synthesis of Monosubstituted *gem*-Difluoroolefins *via* Its Cross-Coupling Reaction.

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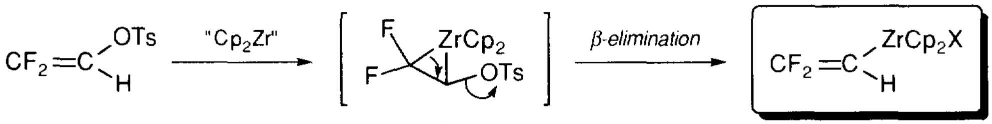
Abstract: *2,2-Difluorovinyl p-toluenesulfonate, readily obtained from 2,2,2-trifluoroethanol, is treated with zirconocene equivalent "Cp_2Zr" to generate the remarkably thermostable nonsubstituted 2,2-difluorovinylzirconocene, which in turn couples with aryl iodides in the presence of palladium catalyst and zinc iodide to afford monosubstituted gem-difluoroolefins in high yields. The reaction proceeds via 2,2-difluorovinylzinc as confirmed by ^{19}F-NMR measurement.* Copyright © 1996 Elsevier Science Ltd

2,2-Difluorovinylmetals provide a straightforward route to synthesize *gem*-difluoroolefins,[1,2b] which are valuable both as building blocks for fluorinated compounds and polymers[2] and as enzyme inhibitors.[3] Most reported 2,2-difluorovinylmetals incorporate an α-position electron-withdrawing group such as oxygen- or sulfur-containing groups, trifluoromethyl, or aryl groups in order to enhance their thermal stability against β-elimination of a metal fluoride.[4] Few 2,2-difluorovinylmetals without a stabilizing substituent have been described; two examples are our recently reported α-alkylated *nonstabilized* 2,2-difluorovinylboranes and -coppers.[5] We are now pursuing *nonsubstituted* 2,2-difluorovinylmetals, which have only two precedents to our knowledge: 2,2-difluorovinyllithium[6] and 2,2-difluorovinylzinc.[7] The preparation of these compounds is complicated by requiring a low temperature (−110 °C) and/or a gaseous starting material. Herein, we report a facile generation of the novel, remarkably thermostable 2,2-difluorovinylzirconocene, and its palladium-catalyzed cross-coupling reaction.

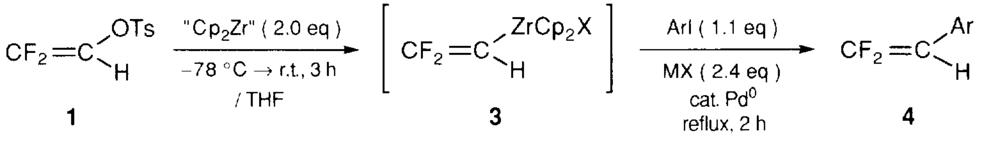
The zirconocene equivalent "Cp_2Zr" is versatile for forming carbon-carbon bonds.[8] The reactions of "Cp_2Zr" with olefins bearing a leaving group proceed through zirconacyclopropane formation and β-elimination to generate organozirconium reagents.[9] If this sequence were applicable to 2,2-difluorovinyl *p*-toluenesulfonate (**1**), the desirable nonsubstituted 2,2-difluorovinylmetal could be generated as shown in Scheme 1.[10] Based on these considerations, we examined the reaction of **1** with "Cp_2Zr" leading to **3**, followed by its coupling reaction with aryl iodides.



1 **2** **3**

Scheme 1

1 was easily obtained from 2,2,2-trifluoroethyl *p*-toluenesulfonate and 2 equiv of butyllithium *via* dehydrofluorination in 90% yield.[11] Thus obtained **1** was successively treated with "Cp_2Zr" (prepared *in situ* from Cp_2ZrCl_2 and 2 equiv of butyllithium)[12] and then *p*-iodonitrobenzene in the presence of catalytic amounts of tris(dibenzylideneacetonyl)bispalladium–chloroform (1/1) ($Pd_2(dba)_3{\bullet}CHCl_3$) and triphenylphosphine. Although **1** was completely consumed, the desired β,β-difluoro-4-nitrostyrene (**4a**) was not obtained. Next, we attempted the transmetalation of **3** to activate the 2,2-difluorovinyl group on zirconium.[13] The effect of metal salts was determined. Cuprous iodide with potassium phosphate as an additive effectively promoted the coupling leading to **4a** in 58% yield (Table 1, Entry 3) and zinc iodide raised the yield of **4a** to 81% (Entry 7).



Scheme 2

Table 1. The effect of metal halides on the coupling reaction of **3** with *p*-$IC_6H_4NO_2$.[a)]

Entry	MX	Yield of **4a** / %[b)]	Entry	MX	Yield of **4a** / %[b)]
1	CuBr	43	5	$ZnCl_2$	75
2	CuI	40	6	$ZnBr_2$	60
3	CuI	58[c)]	**7**	**ZnI_2**	**81**
4	CuCN	36	8	$Zn(OTf)_2$	44

a) 1.1 eq of *p*-$IC_6H_4NO_2$ based on **1** was used. b) GLC yield from **1** relative to internal hexadecane standard. c) 4.0 eq of K_3PO_4 based on **1** was used as an additive.

The coupling reactions with several aryl iodides by using zinc iodide are summarized in Table 2. Aryl iodides bearing either an electron-withdrawing group or an electron-donating group equally provided the corresponding monosubstituted *gem*-difluoroolefins in high yields. The intermediary 2,2-difluorovinylmetals are thermostable, as they did not decompose even though the coupling reactions were performed in THF at reflux. It is also noted that this vinylic arylation using "Cp_2Zr", an aryl iodide, and the palladium catalyst was successfully applied to fluorine-free substrates such as vinyl *p*-toluenesulfonate and phenyl vinyl ether to afford a styrene derivative.[10]

A typical reaction procedure is as follows: To a solution of zirconocene dichloride (150 mg, 0.51 mmol) in THF (2 ml) was added butyllithium (0.65 ml, 1.58 M in hexane, 1.02 mmol) at –78 °C under a nitrogen atmosphere, and the resulting solution was stirred at that temperature for 1 h. A solution of **1** (60 mg, 0.26 mmol) in THF (0.5 ml) was added to the above mixture at –78 °C. After stirring for 5 min, the mixture was warmed to room temperature and stirred for an additional 3 h. Triphenylphosphine (11 mg, 0.041 mmol) and $Pd_2(dba)_3{\bullet}CHCl_3$ (5 mg, 0.005 mmol) were added, and stirring was continued for 10 min. To the resulting mixture were successively added *p*-iodonitrobenzene (70 mg, 0.28 mmol) and zinc iodide (196 mg, 0.61 mmol). After the mixture was heated under reflux for 2 h, phosphate buffer (pH 7) was added to quench the reaction. The usual workup and purification by thin layer chromatography on silica gel (hexane–ethyl acetate 10:1) gave **4a** (36 mg, 76%) as a light yellow liquid.[14]

Table 2. Synthesis of monosubstituted *gem*-difluoroolefins (MX = ZnI_2).

Entry	ArI (1.1 eq)	Product	Yield / %$^{a)}$
1	p-$NO_2C_6H_4I$	**4a**	$81^{b)}$ (76)
2	p-$EtO_2CC_6H_4I$	**4b**	$80^{c)}$ (78)$^{d)}$
3	PhI	**4c**	$71^{c)}$
4	1-NaphthylI	**4d**	$67^{c)}$ (69)$^{e)}$
5	p-$MeOC_6H_4I$	**4e**	$77^{c)}$ (62)

a) Isolated yield from **1** is given in parentheses. b) GLC yield from **1** relative to internal hexadecane standard. c) ^{19}F NMR yield from **1** relative to internal $C_6H_5CF_3$ standard. d) 0.8 eq of aryl iodide based on **1** was used. e) 0.75 eq of aryl iodide based on **1** was used.

In order to confirm 2,2-difluorovinylmetal formation, an ^{19}F-NMR study was conducted on this reaction (Fig. 1). Although the ^{19}F-NMR spectrum of **3** in the reaction mixture was complex, it gave a single peak of 1,1-difluoroethylene (**5**) after protonolysis with aqueous HCl. **3** had three major sets of signals and one of them was observed at 101.6 ppm (dd, J = 46, 18 Hz) and 91.6 ppm (dd, J = 52, 46 Hz), which agreed closely with those of 2,2-difluorovinylzirconocene chloride (**8**) prepared *via* 2,2-difluorovinyllithium (**7**).[6,15] Moreover, treatment of **3** with zinc iodide resulted in a single set of peaks, which are in accordance with those of 2,2-difluorovinylzinc iodide (**6**) prepared by treatment of **7** or **8** with zinc iodide. Thus, these results demonstrate that the above mentioned reaction proceeded as expected *via* 2,2-difluorovinylzirconocene, followed by transmetalation leading to 2,2-difluorovinylzinc. This procedure provides a facile entry to novel 2,2-difluorovinylzirconocene thermostable against β-elimination, which opens a new way to the synthesis of monosubstituted *gem*-difluoroolefins.

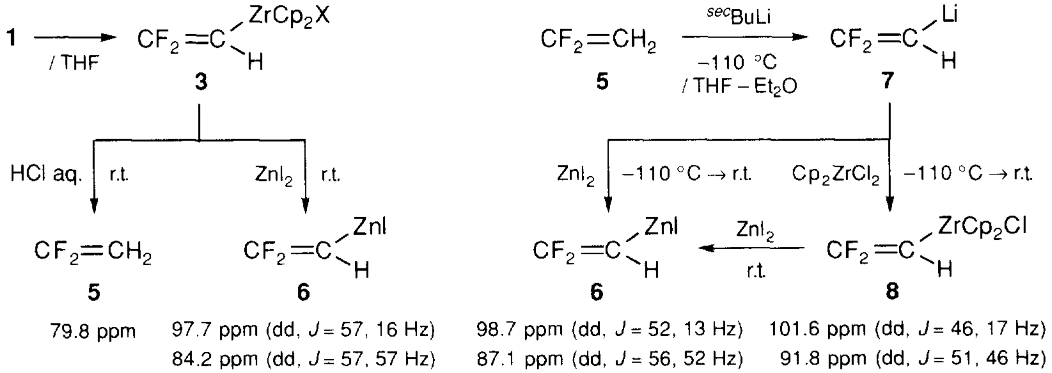


Fig. 1 ^{19}F-NMR study on *gem*-difluorovinylmetals

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14. **4a** (Ar = p-$NO_2C_6H_4$): ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (1H, dd, $J_{HF} = 25.3, 3.4$ Hz), 7.49 (2H, br d, $J = 8.9$ Hz), 8.19 (2H, br d, $J = 8.9$ Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.7 (dd, $J_{CF} = 31, 13$ Hz), 124.1, 128.2 (dd, $J_{CF} = 7, 3$ Hz), 137.4 (t, $J_{CF} = 7$ Hz), 146.5, 157.2 (dd, $J_{CF} = 301, 293$ Hz). ^{19}F NMR (471 MHz, $CDCl_3$ / C_6F_6) 83.1 (1F, dd, $J_{FF} = 19$ Hz, $J_{FH} = 3$ Hz), 84.5 (1F, dd, $J_{FF} = 19$ Hz, $J_{FH} = 25$ Hz) ppm. IR (neat) 1730, 1600, 1515, 1340, 1300, 1250, 1175, 1110, 945, 860, 830, 750, 690 cm^{-1}. MS (70 eV) m/e 185 (M^+; 72), 155 (62), 127 (72), 119 (100), 63 (55). HRMS calcd for $C_8H_5NO_2F_2$ 185.0288 (M^+); found 185.0333.
15. In the reaction of **1**, lithium chloride formed in the preparation of "Cp_2Zr" probably acted as a chloride source to generate **8**.

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