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Vinylic C–F bond activation with low-valent zirconocene: the generation and cross-coupling reactions of 1-fluorovinylzirconocene

Masaki Fujiwara,[†] Junji Ichikawa,[*,†] Tatsuo Okauchi and Toru Minami [*]

Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata, Kitakyushu 804-8550, Japan

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Abstract

(*p*-2,2-Difluorovinyloxyphenyl)dimethylamine, readily obtained from 2,2,2-trifluoroethanol, is treated with zirconocene equivalent 'Cp_2Zr' to generate thermostable 1-fluorovinylzirconocene via a C–F bond cleavage. This 1-fluorovinylzirconocene can be used for C–C bond formation through the cross-coupling with aryl iodides in the presence of palladium catalyst and zinc iodide, leading to (*Z*)-1-aryl-2-(*p*-dimethylaminophenoxy)-1-fluoroolefins in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

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Carbon–fluorine bonds have great strength and consequently their chemical reactivity is restricted. Despite the challenges, considerable progress has been made in the past decade in pursuit of metal-promoted activation and transformation of the C–F bonds in organofluorine compounds.[1] From the viewpoint of synthetic chemistry, however, few examples have been reported on C–F bond cleavage accompanied by C–C bond forming reactions.[1f–h,2]

The zirconocene equivalent 'Cp_2Zr' is a versatile reagent for C–C bond formation starting from olefins with a leaving group.[3] Its reactions proceed through organozirconium species prepared via zirconacyclopropane formation and successive β-elimination of the leaving group. We have recently applied this sequence using 2,2-difluorovinyl *p*-toluenesulfonate **1a** (X=OTs) to generate 2,2-difluorovinylzirconocene **4** through the loss of the tosyloxy group, which could be cross-coupled with aryl iodides to afford *gem*-difluorostyrenes **6**.[4]

Our interest in the C–F bond activation and functionalization next prompted us to investigate the β-elimination of the fluorine substituent instead of the TsO (X) group from the intermediary zirconacyclopropane **2**, which would lead to 1-fluorovinylzirconocene **3** as shown in Scheme 1. Such vinylmetals

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[*] Corresponding authors. Fax: 81-3-5841-4345; e-mail: junji@chem.s.u-tokyo.ac.jp

[†] Present address: Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo, Tokyo 113-0033, Japan

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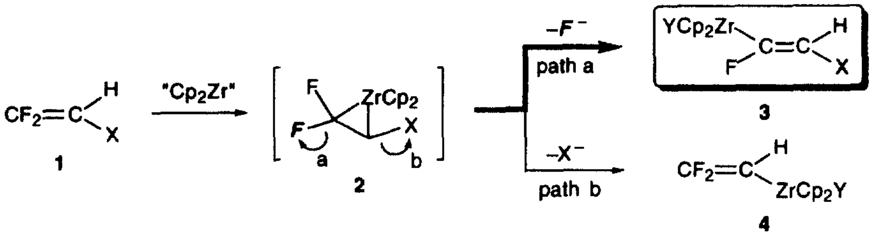
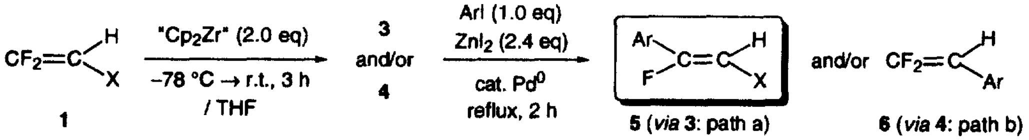
with a fluorine atom at the α-position are, in general, thermally unstable and undergo α-elimination or 1,2-rearrangement.[5,6] Herein we report the facile generation of thermostable 1-fluorovinylzirconocene **3** via vinylic C–F bond cleavage and its use in palladium-catalyzed cross-coupling reactions. This process provides ready access to monofluoroolefins, valuable both as building blocks for selectively fluorinated compounds[7] and as enzyme inhibitors.[8]



Scheme 1.

We have designed starting difluoroolefins that bear a substituent with a lower leaving-group propensity than that of fluorine, so that the preferential elimination of fluoride ion could occur to generate **3**. Initially, screening of substituents (X) was conducted in the reaction of **1** with 'Cp$_2$Zr', followed by the coupling reaction. These starting difluoroolefins were prepared in high yield by the treatment of trifluoroethanol derivatives with 2–3 equiv. of a base such as butyllithium or LDA.[4,9] Thus obtained, **1** was successively treated with 'Cp$_2$Zr' (prepared in situ from Cp$_2$ZrCl$_2$ and 2 equiv. of butyllithium)[10] and then iodobenzene (1 equiv.) in the presence of catalytic amounts of tris(dibenzylideneacetonyl)bispalladium/chloroform (1/1) (Pd$_2$(dba)$_3$·CHCl$_3$) and triphenylphosphine (Scheme 2, Table 1). While **1a** (X=OTs) gave only β,β-difluorostyrene **6**, a mixture of α-fluorostyrene derivative **5** and **6** was obtained in the case of carbamate **1b** (X=OCONEt$_2$). Furthermore, MEM and phenyl ether less reactive to elimination, **1c** and **1d**, exclusively afforded **5** as expected. These results showed that vinylic C–F bond activation was achieved by the β-elimination of fluoride ion from **2** leading to 1-fluorovinylzirconocene **3**,[11] which in turn underwent palladium-catalyzed C–C bond formation.[12] The examined substituent effect on the benzene ring of **1d** revealed that an electron-donating group at the *para*-position effectively promoted the reaction to give **5**. A *p*-dimethylamino group increased the yield of **5** up to 45% (entry 6); the over-reduction product, dimethyl(*p*-(*Z*)-styryloxyphenyl)amine, was also obtained in 12% yield presumably due to the remaining excess 'Cp$_2$Zr'.



Scheme 2.

The coupling reaction of **1f** with several other aryl iodides was conducted as summarized in Table 2. Aryl iodides bearing either an electron-withdrawing or donating group equally afforded the corresponding monofluoroolefins **5f** in good yields. In all cases the *Z* isomer was selectively obtained as the sole product.[13] This stereochemical result demonstrates that the fluoride elimination brings about the selective generation of (*E*)-1-fluorovinylzirconocene **3f**. In addition, **3f** is thermally stable as the coupling reactions proceeded even in refluxing THF.

A typical reaction procedure is as follows: to a solution of zirconocene dichloride (203 mg, 0.69 mmol) in THF (2 ml) was added butyllithium (0.97 ml, 1.43 M in hexane, 1.38 mmol) at –78°C under a nitrogen atmosphere, and the resulting solution was stirred at that temperature for 1 h. A solution of **1f** (69 mg,

Table 1
The effect of substituents on the β-elimination of **2** (Ar=Ph)

Entry	X	Substrate	**5** / %[a)]	**6** / %[a)]
1	TsO	**1a**	0	71[b)]
2	$Et_2NC(O)O$	**1b**	30	14
3	MEMO	**1c**	32	0
4	PhO	**1d**	17	0
5	*p*-$MeOC_6H_4O$	**1e**	39	0
6	*p*-$Me_2NC_6H_4O$	**1f**	45	0

a) ^{19}F NMR yield from **1** relative to internal $C_6H_5CF_3$ standard. b) GLC yield from **1** relative to internal hexadecane standard.

Table 2
Synthesis of 1-substituted 2-aryloxy-1-fluoroolefins **5f** from **1f** ($X=OC_6H_4$*p*-NMe_2)

Entry	ArI[a)]	Product	Yield / %[b)]
1	PhI	**5fa**	63 (53) [45][c)]
2	*p*-$EtO_2CC_6H_4I$	**5fb**	54 (53)
3	*p*-ClC_6H_4I	**5fc**	56 (42)
4	*p*-MeC_6H_4I	**5fd**	75 (67)
5	*p*-$MeOC_6H_4I$	**5fe**	60 (42)
6	1-NaphthylI	**5ff**	75 (62)

a) 0.5 equiv of aryl iodide based on **1f** was used. b) ^{19}F NMR yield from **1f** relative to internal $C_6H_5CF_3$ standard. Isolated yield from **1f** is given in parentheses. c) 1.0 equiv of aryl iodide based on **1f** was used.

0.35 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 (14 mg, 0.055 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (7 mg, 0.007 mmol) were added, and stirring was continued for 10 min. To the resulting mixture were successively added *p*-iodotoluene (37 mg, 0.17 mmol) and zinc iodide (265 mg, 0.83 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 (5:1)) gave **5fd** (31 mg, 67%) as a light yellow oil.[14]

In order to confirm the 1-fluorovinylmetal formation the reaction was monitored by ^{19}F NMR (Fig. 1). Although the ^{19}F NMR spectrum of **3f** in the reaction mixture had three major doublets presumably differing in the ligand (for example Y=F, Cl, or 1-fluorovinyl) on the zirconium, these gave a single set of peaks of (*p*-2-fluorovinyloxyphenyl)dimethylamine **7f** after protonolysis with aqueous HCl. Moreover, treatment of **3f** with zinc iodide resulted in a single doublet, of which protonolysis gave the peaks in accordance with those of **7f**. These results suggest that the above mentioned reaction proceed via 1-fluorovinylzirconocene **3f**, followed by transmetalation leading to 1-fluorovinylzinc **8f**.

In summary, (i) the first example of vinylic C–F bond activation with a low-valent zirconocene has been accomplished in the stereoselective generation of thermostable 1-fluorovinylzirconocene, and (ii) the successive C–C bond formation proceeds in a one-pot operation. This sequence opens a new way to the functionalization of vinylic C–F bonds.

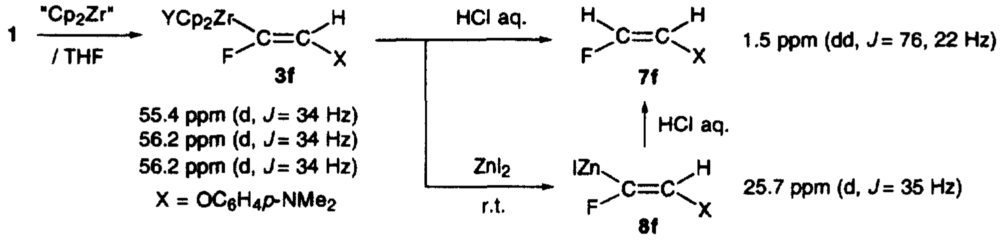


Figure 1. ^{19}F NMR study on 1-fluorovinylmetals (C_6F_6 as an external standard)

Acknowledgements

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13. The configuration of **5fe** (Ar=C_6H_4*p*-OMe) was confirmed by NMR measurement on the basis of the observed NOE between the vinylic proton and the *ortho*-protons of the aryl group (Ar). Stereochemistry was assigned for the other products by the coupling constants between the fluorine and the vinylic proton (J_{FH}=20–23 Hz), which were in accordance with that of **5fe** (20 Hz).
14. **5fd** (X=OC_6H_4*p*-NMe_2, Ar=C_6H_4*p*-Me): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.90 (6H, s), 6.63 (1H, d, J_{HF}=21.4 Hz), 6.72 (2H, dm, J=9.2 Hz), 7.02 (2H, dm, J=9.2 Hz), 7.16 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2, 41.3, 113.9, 117.4, 122.8 (d, J_{CF}=6 Hz), 125.5 (d, J_{CF}=12 Hz), 128.2 (d, J_{CF}=25 Hz), 129.3 (d, J_{CF}=2 Hz), 138.1, 147.4, 147.5 (d, J_{CF}=243 Hz), 149.3. ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) 19.8 (1F, d, J_{FH}=22 Hz) ppm. IR (neat) 2885, 1686, 1512, 1444, 1323, 1232, 1124, 1024, 1011, 879, 818 cm^{-1}. MS (18 eV) *m/e* 271 (M^+; 100). HRMS calcd for $C_{17}H_{18}NOF$ 271.1372 (M^+); found 271.1356.