

Facile Synthesis of β,β -Difluorostyrenes via the Negishi Coupling of Thermally Stable 2,2-Difluorovinyl Zinc–TMEDA Complex

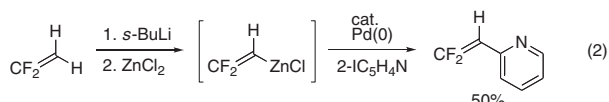
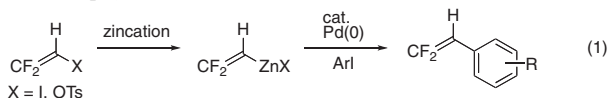
Takeshi Fujita, Tomohiro Ichitsuka, Kohei Fuchibe, and Junji Ichikawa*
 Department of Chemistry, Graduate School of Pure and Applied Sciences,
 University of Tsukuba, Tsukuba, Ibaraki 305-8571

(Received June 13, 2011; CL-110493; E-mail: junji@chem.tsukuba.ac.jp)

2,2-Difluorovinylzinc chloride–TMEDA complex, readily prepared from 1,1-difluoroethylene, undergoes the palladium-catalyzed coupling reaction with aryl halides to afford β,β -difluorostyrenes in high yield. This reaction not only proceeds smoothly with sterically hindered triflates and halides including chlorides, but also exhibits excellent chemoselectivities for multi-halogenated substrates. The intermediary TMEDA complex was found to be thermally stable and storable.

β,β -Difluorostyrenes constitute a major class of compounds in 1,1-difluoro-1-alkenes and have attracted considerable attention, especially as building blocks for fluorine-containing organic molecules¹ and as monomers for functional polymers.² To date several methodologies have been established for the synthesis of β,β -difluorostyrenes. Typically phosphane ylide-based reactions³ and metal-mediated coupling reactions^{4,5} have been used.⁶ While the synthetic methods via phosphane ylide intermediates require arylaldehydes and an excess amount of expensive phosphanes, metal-mediated reactions are more straightforward. Two types of metal-mediated coupling reactions have been developed: coupling reactions between 2,2-difluorovinylmetal reagents and aryl halides (eq 1)⁴ and between arylmetal reagents and difluorovinyl halides.⁵ In both cases, the use of difluorovinyl halides, which are rarely commercially available, is required.

In 1985, Sauvêtre and Normant achieved the preparation of a difluorovinylzinc reagent directly from commercially available 1,1-difluoroethylene, the smallest compound in the 1,1-difluoro-1-alkene family, by sequential lithiation and zincation.⁷ They applied this reagent to the palladium-catalyzed coupling reaction with heteroaryl halides, albeit in low yield (eq 2).^{7b} The low yield obtained was probably due to the poor stability of the intermediary difluorovinylzinc chloride in the presence of a lithium salt.^{8,9} Herein we report the preparation of a thermally stable difluorovinylzinc reagent by complexation with *N,N,N',N'*-tetramethylethylenediamine (TMEDA), which allows the efficient synthesis of β,β -difluorostyrenes via the palladium-catalyzed Negishi coupling reaction (eq 3).¹⁰



Typically, organozinc reagents are known to be often stabilized by coordination of two amine molecules.¹¹ This

Table 1. Screening of amine ligands for preparation of the zinc reagent

Entry	ZnX ₂ (x equiv)	Amine ligand (y equiv)	Yield/% ^a
1	ZnCl ₂ (1.0)		50
2	ZnCl ₂ (1.0)	NMP (2.6)	9
3	ZnCl ₂ (1.0)	Pyridine (2.6)	36
4	ZnCl ₂ (1.0)	NEt ₃ (2.6)	70
5	ZnCl ₂ (1.0)	DABCO (1.3)	0
6	ZnCl ₂ (1.0)	TMEDA (1.3)	90
7 ^b	ZnCl ₂ (1.0)	TMEDA (1.3)	95
8 ^b	ZnI ₂ (1.0)	TMEDA (1.3)	70
9	ZnCl ₂ ·TMEDA (1.0)		62

^aYields are determined by ¹⁹F NMR using PhCF₃ as an internal standard. ^bLithiation was carried out in the presence of TMEDA.

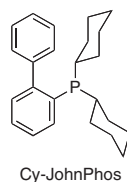
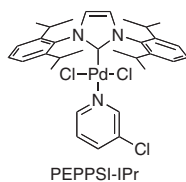
motivated us to seek an appropriate choice of amines to construct a thermally stable 2,2-difluorovinylzinc complex as a manageable reaction intermediate. We first reviewed the previously reported conditions in which no ligands were employed.^{7b} The conditions furnished 2,2-difluorovinylzinc chloride in 50% yield (Table 1, Entry 1). The main reason for the low yield might be due to the decomposition of 2,2-difluorovinylzinc chloride to fluoroacetylene.^{8,9} Next we screened monodentate amine ligands (2.6 equiv) as additives. Use of NMP and pyridine decreased the yield of the corresponding complexes **2** (Entries 2 and 3), whereas NEt₃ marginally enhanced the formation of **2** (Entry 4). While 1,4-diazabicyclo[2.2.2]octane (DABCO), which can act as an exobidentate ligand, prevented the process (Entry 5), addition of TMEDA turned out to be highly effective for the formation of **2** (Entries 6–9).^{12,13} The best result (95% yield) was obtained when *s*-BuLi was added to the mixture of **1** and TMEDA, followed by addition of ZnCl₂ (Entry 7).¹⁴ The obtained zinc–TMEDA complex **2a** is thermally stable and thus storable.

Having prepared thermally stable difluorovinylzinc–TMEDA complex **2a**, its palladium-catalyzed Negishi coupling was examined using a wide variety of aryl halides and pseudohalides (Table 2). Aryl iodides **3a–3d**, aryl bromide **3e**, and aryl triflate **3f** participated in the coupling reaction to produce difluorostyrenes **4a–4f**, respectively, in high yield (Entries 1–6).^{15,16} In the reaction of **3g–3j**, PEPPSI-IPr was used as an electron-rich palladium catalyst or Cy-JohnPhos as an electron-rich ligand (Entries 7–10).^{17,18} Sterically hindered *ortho*-monosubstituted substrate **3g** (Entry 7) and *ortho*-disubstituted substrates **3h** and **3i** (Entries 8

Table 2. Difluorostyrene synthesis with difluorovinylzinc-TMEDA

Entry	Ar-X	Pd catalyst (mol %)	Time/h	Yield/% ^a
1	(<i>p</i> -Me) 3a	[Pd(PPh ₃) ₄] (2)	6	59 (86), 4a
2	(<i>p</i> -OMe) 3b	[Pd(PPh ₃) ₄] (2)	6	87, 4b
3	(<i>o</i> -NH ₂) 3c	[Pd(PPh ₃) ₄] (2)	1	87, 4c
4 ^b	(<i>p</i> -NO ₂) 3d	[Pd ₂ (dba) ₃] (2)/PPh ₃ (8)	12	84, 4d
5	3e	[Pd(PPh ₃) ₄] (2)	10	87, 4e
6	3f	[Pd(PPh ₃) ₄] (2)	6	90, 4f
7	3g	PEPPSI-IPr (5)	10	82, 4g
8	3h	PEPPSI-IPr (4)	12	79, 4h
9	3i	[Pd ₂ (dba) ₃] (2.5)/ Cy-JohnPhos (10)	24	(59), 4i
10	3j	PEPPSI-IPr (5)	8	(71), 4g

^aIsolated yield. In parentheses are shown yields determined by ¹⁹F NMR using PhCF₃ as an internal standard. ^bRoom temperature.



and 9)¹⁶ successfully underwent the coupling reaction. Even the reaction of aryl chloride **3j** efficiently proceeded to give **4g** in good yield (Entry 10).

It is noteworthy that the reaction exhibited complete chemoselectivity (Table 3). Both 3-iodophenyl triflate (**3k**) and 3-bromo-4-iodobiphenyl (**3l**) showed thorough selective substitution of the iodo group (Entries 1 and 2). Likewise, the triflyloxy groups of **3m** and **3n** were exclusively substituted over the chlorine atoms (Entries 3 and 4). In the case of 3-bromophenyl triflate (**3o**), the triflyloxy group reacted preferentially (>85% selectivity), although triflates and bromides generally show similar reactivity toward transition-metal-catalyzed coupling reactions (Entry 5). As a result, the relative reactivity of aryl halides and pseudohalides was found to be in the order of I > OTf > Br > Cl.¹⁹

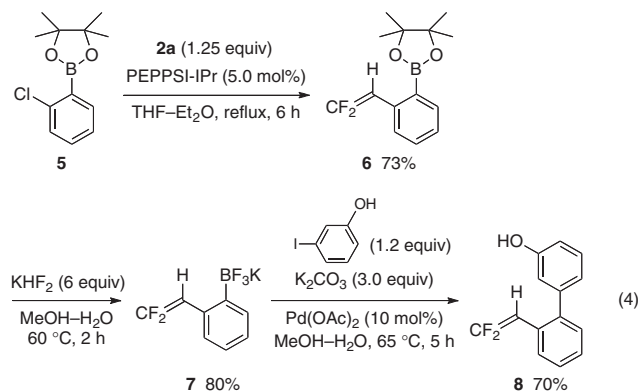
Intriguingly, even a boronate ester moiety was tolerated in this coupling reaction. Boronate ester **5** bearing a chlorine atom was reacted with the difluorovinylzinc-TMEDA complex **2a** to give the corresponding difluorostyrene **6** in high yield without the

Table 3. Chemoselectivity in the coupling reaction of **2a**

Entry	Ar-X	Yield/% ^a
1 ^b	3k	92, 4k
2 ^c	3l	96, 4l
3 ^d	3m	73, 4m
4 ^e	3n	87, 4n
5 ^f	3o	69 (71), ^g 4o

^aIsolated yield. In parentheses are shown yields determined by ¹⁹F NMR using PhCF₃ as an internal standard. ^bReaction conditions: [Pd₂(dba)₃] (2.5 mol %), P(2-furyl)₃ (10 mol %), rt, 4 h. ^c[Pd₂(dba)₃] (2.5 mol %), P(2-furyl)₃ (10 mol %), 55 °C, 4 h. ^d[PdCl₂(dppp)] (5 mol %), LiCl (375 mol %), reflux, 23 h. ^e[PdCl₂(dppf)] (4 mol %), reflux, 12 h. ^f[Pd₂(dba)₃] (2.5 mol %), dppb (5 mol %), 45 °C, 24 h. ^gBy-products formed by the reaction of the bromo group were observed by ¹⁹F NMR (10% in total).

formation of any self-Suzuki-Miyaura coupling products (eq 4). The subsequent transformation of boronate **6** into trifluoroborate **7** followed by the subsequent Suzuki-Miyaura coupling with 3-iodophenol afforded the desired coupling product **8**. The direct Negishi coupling of **2a** and 2'-halobiphenyl-3-ol cannot produce **8**, because the zinc reagent undergoes protonolysis with a phenolic hydroxy group. However, the outstanding chemoselectivity of the zinc-mediated difluorovinylation compensates this limitation.



In conclusion, we have disclosed a facile approach to β,β -difluorostyrenes from 1,1-difluoroethylene via the palladium-catalyzed coupling of the thermally stable 2,2-difluorovinylzinc chloride–TMEDA complex **2a**. The high functional group tolerance and the elegant chemoselectivity of the reaction would facilitate the construction of a library of various β,β -difluorostyrenes. The zinc–TMEDA complex **2a** has proven to be storable, and thus is an excellent reagent for introducing the difluorovinyl group.

This research was supported in part by Grant-in-Aid for Scientific Research from MEXT, Japan. We acknowledge Central Glass Co., Ltd. for the generous gift of 1,1-difluoroethylene.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

References and Notes

- 1 K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, UK, **2006**, Chap. 1, pp. 60–67; K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, UK, **2006**, Chap. 2, pp. 112–121.
- 2 R. Souzy, B. Ameduri, B. Boutevin, *Prog. Polym. Sci.* **2004**, *29*, 75.
- 3 a) S. A. Fuqua, W. G. Duncan, R. M. Silverstein, *J. Org. Chem.* **1965**, *30*, 1027. b) S. A. Fuqua, W. G. Duncan, R. M. Silverstein, *Org. Synth. Coll. Vol.* **1973**, *5*, 390. c) S.-i. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Nae, H. S. Kesling, *Chem. Lett.* **1979**, 983. d) M. Obayashi, E. Ito, K. Matsui, K. Kondo, *Tetrahedron Lett.* **1982**, *23*, 2323. e) P. S. Bhadury, M. Palit, M. Sharma, S. K. Raza, D. K. Jaiswal, *J. Fluorine Chem.* **2002**, *116*, 75. f) I. Nowak, M. J. Robins, *Org. Lett.* **2005**, *7*, 721.
- 4 a) J. Ichikawa, M. Fujiwara, H. Nawata, T. Okauchi, T. Minami, *Tetrahedron Lett.* **1996**, *37*, 8799. b) B. V. Nguyen, D. J. Burton, *J. Org. Chem.* **1997**, *62*, 7758. c) J. Ichikawa, *J. Fluorine Chem.* **2000**, *105*, 257. d) A. Raghavanpillai, D. J. Burton, *J. Org. Chem.* **2006**, *71*, 194.
- 5 T. M. Gøgsig, L. S. Søjberg, A. T. Lindhardt, K. L. Jensen, T. Skrydstrup, *J. Org. Chem.* **2008**, *73*, 3404.
- 6 For other approaches to β,β -difluorostyrene, see: a) V. G. Nenajdenko, G. N. Varseev, V. N. Korotchenko, A. V. Shastin, E. S. Balenkova, *J. Fluorine Chem.* **2003**, *124*, 115. b) G. K. S. Prakash, Y. Wang, J. Hu, G. A. Olah, *J. Fluorine Chem.* **2005**, *126*, 1361. c) M. Pohmakotr, K. Boonkitpattarakul, W. Ieawsuwan, S. Jarussophon, N. Duangdee, P. Tuchinda, V. Reutrakul, *Tetrahedron* **2006**, *62*, 5973. d) Y. Zhao, W. Huang, L. Zhu, J. Hu, *Org. Lett.* **2010**, *12*, 1444.
- 7 a) J.-P. Gillet, R. Sauvêtre, J.-F. Normant, *Tetrahedron Lett.* **1985**, *26*, 3999. b) J. P. Gillet, R. Sauvêtre, J. F. Normant, *Synthesis* **1986**, 538.
- 8 Fluoroacetylenes have been prepared by lithiation of 1,1-difluoroethylene. See: T. Hanamoto, Y. Koga, T. Kawanami, H. Furuno, J. Inanaga, *Angew. Chem., Int. Ed.* **2004**, *43*, 3582.
- 9 Without any lithium salts, fluoroacetylenes are hardly produced from 2,2-difluorovinylzinc species. See ref. 4.
- 10 For a recent review on the Negishi coupling, see: E.-i. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71.
- 11 H. Schumann, S. Freitag, F. Girgsdies, H. Hemling, G. Kociok-Köhn, *Eur. J. Inorg. Chem.* **1998**, 245, and references cited therein.
- 12 An equimolar amount of TMEDA could not complete the complexation.
- 13 The formation of **2a** was supported by the ^{19}F NMR (470 MHz) spectra of the reaction mixture. The data are shown below (δ : parts per million from hexafluorobenzene). **2a**: δ 87.9 (1F, dd, $J_{\text{FF}} = 58$ Hz, $J_{\text{FH}} = 58$ Hz), 98.7 (1F, dd, $J_{\text{FF}} = 58$ Hz, $J_{\text{FH}} = 15$ Hz). cf. 2,2-Difluorovinylzinc chloride: δ 86.2 (1F, dd, $J_{\text{FF}} = 55$ Hz, $J_{\text{FH}} = 55$ Hz), 98.5 (1F, dd, $J_{\text{FF}} = 55$ Hz, $J_{\text{FH}} = 14$ Hz). 1,1-Difluoroethylene: δ 80.0–80.2 (m).
- 14 To a solution of TMEDA (98 μL , 0.65 mmol) in THF (2.0 mL) and diethyl ether (0.50 mL) at -110°C was slowly added gaseous 1,1-difluoroethylene (14.5 mL, 0.60 mmol) via syringe, and the mixture was stirred at the same temperature for 5 min. To the solution at -110°C was slowly added *s*-BuLi (0.96 M in hexane, 0.52 mL, 0.50 mmol) and the mixture was stirred at the same temperature for 20 min. To the reaction mixture at -110°C was added a THF solution of anhydrous ZnCl_2 (1.00 M, 0.50 mL, 0.50 mmol). After the reaction mixture was stirred at -100°C for 30 min, a THF–ether solution of **2a** was obtained as a colorless solution (0.48 mmol, 95%: The yield and the concentration were determined by ^{19}F NMR using PhCF_3 as an internal standard).
- 15 In a two-necked flask was placed the prepared THF–ether solution of **2a** (0.125 M, 7.6 mL, 0.95 mmol). To the solution were added a solution of 4-iodoanisole (**3b**, 189 mg, 0.81 mmol) in THF (1.5 mL) and $[\text{Pd}(\text{PPh}_3)_4]$ (17 mg, 15 μmol). After refluxing for 6 h, the reaction mixture was filtered through a pad of silica gel (diethyl ether). The filtrate was concentrated under reduced pressure and purified by preparative thin layer chromatography (silica gel, pentane:diethyl ether = 20:1) to give **4b** (119 mg, 87%) as a colorless liquid.
- 16 Difluorostyrene **4a** was difficult to isolate in high yield because of its volatility. Difluorostyrene **4i** and unreacted iodide **3i** were inseparable by distillation and column chromatography.
- 17 PEPPSI-IPr is known as an efficient catalyst for the Negishi coupling. For reviews, see: a) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem.—Eur. J.* **2006**, *12*, 4749. b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem., Int. Ed.* **2007**, *46*, 2768. c) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, 4343.
- 18 Cy-JohnPhos is a Buchwald ligand, which is used for various coupling reactions of sterically hindered substrates. For a review, see: R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.
- 19 For several examples on chemoselective coupling reactions, see: a) M. Rottländer, N. Palmer, P. Knochel, *Synlett* **1996**, 573. b) T. Kamikawa, T. Hayashi, *Tetrahedron Lett.* **1997**, *38*, 7087. c) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.