Cross-Coupling Reactions of (*Z*)-2-Fluoro-2-trifluoromethylethenyl Tosylate with Aryl- and Arylethenylboronic Acids

Yeong Hyun Jin, Seo Hee Lee, Sung Lan Jeon, and In Howa Jeong*

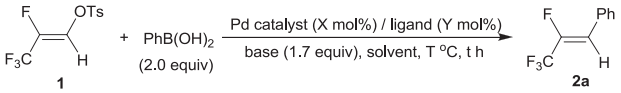
Department of Chemistry and Medical Chemistry, Yonsei University, Wonju 220-710, South Korea.
**E-mail: jeongih@yonsei.ac.kr*
Received October 31, 2017, Accepted February 6, 2018, Published online March 23, 2018

Keywords: Cross-coupling reaction, (*Z*)-2-Fluoro-2-trifluoromethylethenyl tosylate, Arylboronic acids, Arylethenylboronic acids

Organofluorine compounds have received much attention in medicinal, agricultural, and material sciences because they often confer dramatic changes in their chemical, physical, and biological properties.[1–3] Especially, compounds containing trifluoromethyl group have been widely applied in drug development because of their unique property for the high cross ability of the cell membrane.[4–6] Therefore, introduction of a trifluoromethyl group into the organic molecules has been an important subject in recent years.[7–11] Although methods for the trifluoromethylation involving a direct coupling reaction of trifluoromethylated metal reagents with aryl- or alkenyl halides have been well established in recent years,[12–14] these methods suffer from low reactivity and low selectivity. An alternative promising approach is to use trifluoromethylated building blocks which can be easily prepared from the commercially available starting materials. In our continuing efforts to explore the preparation of trifluoromethylated alkenes, we are interested in the highly stereoselective preparation of trifluoromethylated alkenes by cross-coupling reaction of the organometallic reagents with the corresponding stereocontrolled trifluoromethylated alkene. Recently, we established the effective cross-coupling reactions between several 2,2-difluoroethenyl tosylate derivatives having two fluorine atoms at the one carbon atom of the double bond and organometallic reagents, in which direct cross-coupling reaction of tosyl group with arylstannane reagents[15,16] or arylboronic acids,[17] and transformation of tosyl group to stannane group[18,19] for the Stille cross-coupling reactions were described. We will extend this study to the cross-coupling reaction of trifluoromethylated alkenyl tosylate. Since trifluoromethylated ethenyl system is totally different from 1,1-difluorinated ethenyl one from the electronic distribution point of view, examination of this coupling reaction will be valuable. The only one case of trifluoromethylated alkenyl tosylate was reported by Funabiki *et al*. who prepared the highly (*Z*)-stereoselective 2-fluoro-2-trifluoromethylethenyl tosylate and then carried out reactions with a variety of electrophiles after *in situ* generation of the corresponding perfluoroethenyllithium reagent.[20] However, the direct cross-coupling reaction of (*Z*)-2-fluoro-2-trifluoromethylethenyl tosylate with organometallic reagents has not been studied and also their products have not been easily prepared by the previous methods.[21–23] Herein, we wish to report the general and efficient preparation of highly stereoselective (*Z*)-(2,3,3,3-tetrafluoroprop-1-enyl)benzenes and (*Z,E*)-4-aryl-1-fluoro-1-trifluoromethylbuta-1,3-dienes via the cross-coupling reactions of (*Z*)-2-fluoro-2-trifluoromethylethenyl tosylate with aryl- and arylethenylboronic acids.

Starting material, the highly (*Z*)-stereoselective 2-fluoro-2-trifluoromethylethenyl tosylate (**1**) (*Z:E* = 98:2) was prepared by the previous procedure.[20] Then, we first examined the reactivity of **1** with tributylphenylstannane in the presence of $Pd(PPh_3)_4$ (5 mol %) and LiBr (3 equiv) in DMF at 100°C for 2 h, which condition was performed for the preparation of 1,1-diaryl-2,2-difluoroethenes,[15] but the reaction did not proceed at all. Then, we changed the organometallic reagent to less toxic phenylboronic acid. When **1** was treated with phenylboronic acid (2.0 equiv) in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %) and Cs_2CO_3 (1.7 equiv) in MeOH at room temperature for 12 h, the desired product **2a** was not observed at all. The use of Pd catalysts such as $Pd(OAc)_2$ or $Pd_2(dba)_3$ in the same reaction did not provide the desired product, either. However, treatment of **1** with phenylboronic acid (2.0 equiv) in the presence of $Pd(OAc)_2$ (2 mol %), PCy_3 (4 mol %) and Cs_2CO_3(1.7 equiv) in a mixture of dioxane and water (20:1) at 100°C for 4 h resulted in the formation of coupled product **2a** in 23% yield based on the conversion of starting material. This result indicated that the use of bulky ligand such as PCy_3 and the use of H_2O as a co-solvent caused to proceed the coupling reaction. However, the bulky ligand such as X-Phos was not effective in this reaction. The use of K_3PO_4 as a base in the same reaction caused to increase the yield **2a** up to 32% yield. More addition of the mol % of $Pd(OAc)_2$ and PCy_3 resulted in the increase in the yield of **2a**. Finally, when **1** was reacted with phenylboronic acid (2.0 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %) and K_3PO_4(1.7 equiv) in a mixture of dioxane and water (20:1) at 100°C for 4 h, the desired product **2a** was obtained in 80% yield. The use of less amount of

Table 1. Optimization for the formation of the coupled product **2a**.



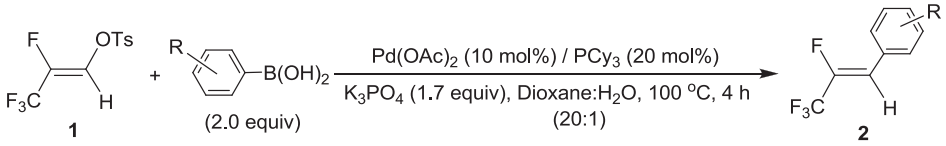
Entry	Pd Catalyst (X)	Ligand (Y)	Base	Solvent	T(°C)	t(h)	Yield (%)[a]
1	$Pd(PPh_3)_2Cl_2$ (5)	—	Cs_2CO_3	MeOH	25	12	0
2	$Pd_2(dba)_3$ (5)	—	Cs_2CO_3	MeOH	25	12	0
3	$Pd(OAc)_2$ (5)	—	Cs_2CO_3	MeOH	25	12	0
4	$Pd(OAc)_2$ (2)	PCy_3 (4)	Cs_2CO_3	Dioxane/H_2O(20/1)	100	4	23
5	$Pd(OAc)_2$ (2)	PCy_3 (4)	Na_2CO_3	Dioxane/H_2O(20/1)	100	4	15
6	$Pd(OAc)_2$ (2)	PCy_3 (4)	K_3PO_4	Dioxane/H_2O(20/1)	100	4	32
7	$Pd(OAc)_2$ (2)	X-Phos (4)	K_3PO_4	Dioxane/H_2O(20/1)	100	4	0
8	$Pd(OAc)_2$ (2)	PCy_3 (4)	K_3PO_4	Dioxane/H_20 (10/1)	100	4	21
9	$Pd(OAc)_2$ (4)	PCy_3 (8)	K_3PO_4	Dioxane/H_2O(20/1)	100	4	45
10	$Pd(OAc)_2$ (6)	PCy_3(12)	K_3PO_4	Dioxane/H_2O(20/1)	100	4	52
11	$Pd(OAc)_2$(10)	PCy_3 (20)	K_3PO_4	Dioxane/H_2O(20/1)	100	4	80
12	$Pd(OAc)_2$(15)	PCy_3 (30)	K_3PO_4	Dioxane/H_2O(20/1)	100	4	64

[a] Isolated yield.

phenylboronic acid gave the result of low yield of **2a** and long reaction time. The results of the optimization for the formation of **2a** were summarized in Table 1.

The optimized reaction condition was applied to prepare a variety of the coupled products **2**. Therefore, the reactions of **1** with a variety of arylboronic acids having electron-withdrawing group such as fluoro, chloro, or trifluoromethyl as well as electron-donating group such as methyl or methoxy on the *ortho*-, *meta*-, or *para*-position of benzene ring under the optimized reaction condition gave the corresponding highly stereoselective (*Z*)-(2,3,3,3-tetrafluoroprop-1-enyl)benzenes **2a–j** in 54–80% yields. Aryl boronic acids substituted by electron-donating groups on the benzene ring provided relatively higher yields of **2** than aryl boronic acids substituted by electron-withdrawing groups on the benzene ring. Steric effect did not affect on this coupling reaction. We also prepared (*Z,E*)-4-aryl-1-fluoro-1-trifluoromethylbuta-1,3-dienes **3a–f** in 50–75% yields from the cross-coupling reaction of **1** with *(E)*-2-arylethenylboronic acid under the same reaction condition. Assignment of (*Z*)-isomer of **2a** was established by *trans* H—F coupling constant (J = 36.0 Hz) and stereochemistry of **3a** was assigned by *trans* H—F coupling constant (J = 31.6 Hz) and *trans* H—H coupling constant (J = 15.6 Hz) in ^{1}H and ^{19}F NMR spectrum. The results of the coupling reactions between **1** and arylboronic acids and

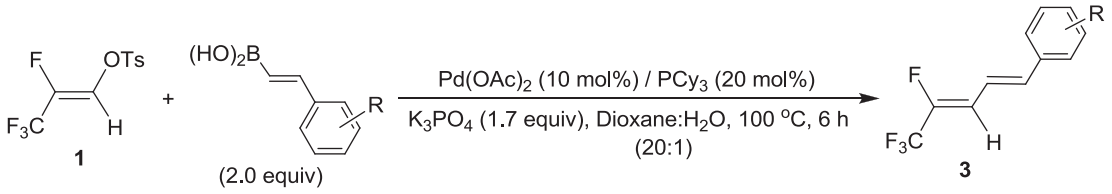
Table 2. The coupling reaction of **1** with arylboronic acids.



Compound	R	Yield (%)[a]
2a	H	80
2b	*p*-F	54
2c	*p*-CI	56
2d	*p*-CH_3	73
2e	*p*-OCH_3	75
2f	*p*-CF_3	60
2g	*m*-CI	55
2h	*m*-CH_3	75
2i	*m*-OCH_3	70
2j	*o*-CH3	62

[a] lsolated yield.

Table 3. The coupling reaction of **1** with arylethenylboronic acids.



Compound	R	Yield (%)[a]
3a	H	75
3b	*p*-F	52
3c	*p*-Cl	55
3d	*p*-CH_3	66
3e	*p*-OCH_3	68
3f	*m*-F	50

[a] lsolated yield.

(E)-2-arylethenylboronic acid were summarized in Tables 2 and 3, respectively.

In summary, we have developed a general and efficient method for the preparation of (*Z*)-(2,3,3,3-tetrafluoroprop-1-enyl)benzenes **2a–j** and (*Z,E*)-4-aryl-1-fluoro-1-trifluoromethyl buta-1,3-dienes **3a–f** in moderate to high yields from the palladium-catalyzed cross-coupling reactions of (*Z*)-2-fluoro-2-trifluoromethylethenyl tosylate (**1**) with arylboronic acids or arylethenylboronic acids. This is the first example of Suzuki-Miyaura cross-coupling reaction in the trifluoromethylated alkenyl tosylate system.

Experimental

Instrumentation and Chemicals. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCEII^{++} NMR spectrometer with tetramethylsilane (TMS) as an internal standard and ^{19}F NMR spectra were also recorded on a 400 MHz Bruker AVANCEII^{++} NMR spectrometer (Billerica, MA, USA) with $C_6H_5CF_3$ (−63.72 ppm from $CFCl_3$) as an internal standard and the upfield as negative. All chemical shifts (δ) are expressed in parts per million and coupling constants (*J*) are given in Hertz. Mass spectra were obtained by using Agilent Technologies 6890 N GC/5973 Network MSD (EI, 70 eV; Santa Clara, CA, USA). Commercially available reagents were purchased from Aldrich (Seoul, Korea), Lancaster (London, UK), Tokyo Kasei (Tokyo, Japan) and Fluorochem (Karlsruhe, Germany). All solvents were dried by general purification method. Flash chromatography was performed on 40–60 m silica gel (230–400 mesh).

General Procedure for the Preparation of (*Z*)-(2,3,3,3-Tetrafluoroprop-1-Enyl)Benzenes 2. A 10 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and nitrogen tee connected to an argon source was charged with $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), K_3PO_4 (6.0 mmol) and 1 mL of dioxane/H_2O (20/1). The solution of **1** (0.10 g, 0.35 mmol) and arylboronic acid (0.70 mmol) dissolved in 3 mL of dioxane/H_2O (20/1) was added into the reaction mixture. After the reaction mixture was refluxed at 100°C for 4 h and then cooled to room temperature, the mixture was quenched with water. The reaction mixture was extracted with ether (30 mL) twice, dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with *n*-hexane and ethyl acetate (20:1) provided (*Z*)-(2,3,3,3-tetrafluoroprop-1-enyl)benzenes **2.**

Spectral Data for the Compounds 2. (*Z*)-(2,3,3,3-Tetrafluoroprop-1-enyl)benzene (2a): 2a was prepared in 80% yield (0.052 g) according to the general procedure. **2a** is a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.56 (m, 2H), 7.42–7.40 (m, 3H), 6.36 (d, J = 36.0 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$): δ −73.06 (d, J = 11.3 Hz, 3F), −133.04 (dq, J = 36.0, 11.3 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2 (dq, J = 266, 38 Hz), 130.0, 129.9, 129.8, 129.0, 119.1 (dq, J = 269, 40 Hz), 111.7 (m); MS *m/z* (relative intensity) 190 (M^+, 100), 169 (18), 151 (33), 140 (53), 120 (19), 101 (28), 75 (22), 69 (26), 51 (26).

General Procedure for the Preparation of (*Z,E*)-4-Aryl-1-fluoro-1-trifluoromethylbuta-1,3-Dienes. A 10 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and nitrogen tee connected to an argon source was charged with $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), K_3PO_4 (6.0 mmol) and 1 mL of dioxane/H_2O (20/1). The solution of **1** (0.10 g, 0.35 mmol) and trans-2-arylvinylboronic acid (0.70 mmol) dissolved in 3 mL of dioxane/H_2O (20/1) was added into the reaction mixture. After the reaction mixture was refluxed at 100°C for 6 h and then cooled to room temperature, the mixture was quenched with water. The reaction mixture was extracted with ether (30 mL) twice, dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with *n*-hexane and ethyl acetate (20:1) provided (*Z,E*)-4-aryl-1-fluoro-1-trifluoromethyl-1,3-butadienes **3.**

Spectral Data for the Compounds 3. (*Z,E*)-1-Fluoro-1-trifluoromethyl-4-phenylbuta-1,3-diene (3a): **3a** was prepared in 75% yield (0.064 g) according to the general procedure. **3a** is a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.45 (m, 2H), 7.37–7.31 (m, 3H), 6.94 (dd, J = 15.6, 10.8 Hz, 1H), 6.74 (d, J = 15.6 Hz, 1H), 6.42 (dd, J = 31.6, 10.8 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$): δ −72.86 (d, J = 15.0 Hz, 3F), −135.50 (dq, J = 32.0, 15.1 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8 (dq, J = 262, 39 Hz), 138.5, 136.0, 134.9, 129.3, 129.0, 127.3, 119.1 (dq, J = 269, 40 Hz), 112.6 (m); MS *m/z* (relative intensity) 216 (M^+, 43), 177 (7), 147 (100), 146 (65), 127 (28), 115 (8), 82 (9), 75 (7), 69 (7), 63 (7), 51 (15).

Acknowledgments. This study was supported by a grant of the Korean Health Technology R & D Project, Ministry of Health & Welfare, Republic of Korea. (Grant No. HN13C0070).

Supporting Information. Additional supporting information is available in the online version of this article.

References

1. J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, NY, **1991**.
2. I. Ojima, J. R. McCarthy, J. T. Welch, *Biomedical Frontiers of Fluorine Chemistry*, American Chemical Society, Washington DC, **1996**.
3. K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, **2006**.
4. W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359.
5. N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529.
6. X. Shao, C. Xu, L. Lu, Q. Shen, *Acc. Chem. Res.* **2015**, *48*, 1227.
7. H. Liu, Z. H. Gu, X. F. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 617.
8. T. Liang, C. N. Neumann, T. Litter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.
9. L. L. Chu, F. L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513.
10. J. Charpentier, N. Fruh, A. Togni, *Chem. Rev.* **2015**, *115*, 650.
11. X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683.
12. S. Roy, B. T. Gregg, G. W. Gribble, V. D. Le, *Tetrahedron* **2011**, *67*, 2161.
13. Y. Mace, E. Magnier, *Eur. J. Org. Chem.* **2012**, *2479*.
14. J. Nie, H. C. Guo, D. Cahard, J. A. Ma, *Chem. Rev.* **2011**, *111*, 455.
15. S. Y. Han, I. H. Jeong, *Org. Lett.* **2010**, *12*, 5518.
16. J. H. Kim, Y. R. Jeong, S. L. Jeon, I. H. Jeong, *J. Fluor. Chem.* **2014**, *167*, 166.
17. J. H. Kim, S. J. Choi, I. H. Jeong, *Beilstein J. Org. Chem.* **2013**, *9*, 2470.
18. S. Y. Han, H. Y. Lee, J. H. Jeon, I. H. Jeong, *Tetrahedron Lett.* **2012**, *53*, 1833.
19. J. H. Jeon, J. H. Kim, Y. J. Jeong, I. H. Jeong, *Tetrahedron Lett.* **2014**, *55*, 1292.
20. K. Funabiki, T. Ohtsuki, T. Ishihara, H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2413.
21. W. Dmowski, *J. Fluor. Chem.* **1985**, *29*, 273.
22. W. R. Dolbier, T. A. Gray, K. Onnishi, *Synthesis* **1987**, *10*, 956.
23. I. H. Jeong, M. S. Kim, Y. S. Park, *Bull. Korean Chem. Soc.* **2002**, *23*, 1823.

