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Monofluorovinyl Tosylate: A Useful Building Block for the Synthesis of Terminal Vinyl Monofluorides via Suzuki−Miyaura Coupling

He Zhang, Chang-Bing Zhou, Qing-Yun Chen, Ji-Chang Xiao,* and Ran Hong*

Key Laboratory of Organofluorine Chemistry and Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

jchxiao@sioc.ac.cn; rhong@sioc.ac.cn

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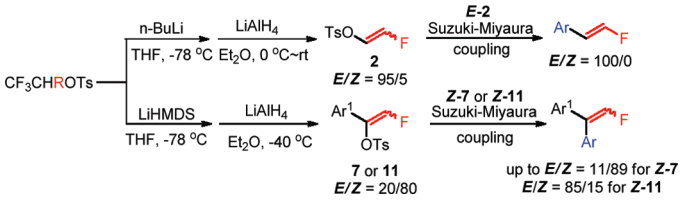
ABSTRACT



Monofluorovinyl tosylate was developed as a practical vinyl fluoride building block to couple with a variety of arylboronic acids in the presence of a palladium catalyst. The high stereoselectivity of 2-aryl-1-fluoroethene derivatives was achieved. This approach is also applicable to the synthesis of 2,2-diaryl-1-fluoroethenes in good yields.

It has been known that fluorinated compounds are the least abundant natural organohalides.[1] Due to their unique properties such as hydrophobicity and metabolic stability, fluorinated compounds have been widely utilized in drugs, polymers, liquid crystals, and so on.[2] Terminal vinyl fluorides are one of the most important fluorinated organic compounds, especially for mimicking the peptide bond, often possessing spectacular characteristics in comparison with their hydrogen analogs. Robins and co-workers reported that 5′-fluoro-4′,5′-didehydro-Ei′-deoxyadenosine (ZFDDA) and its derivatives exhibited effective antivirus and enzyme inhibitory activities.[3] Vinyl fluorides can also be copolymerized with ethylene by palladium-mediated catalysis, as reported by Jordan.[4] Experimental and theoretical investigations carried out by Haufe and Würthwein indicated a profound effect of vinyl fluorides in the Diels−Alder reaction of α- or β-fluorostyrenes with typical dienes.[5]

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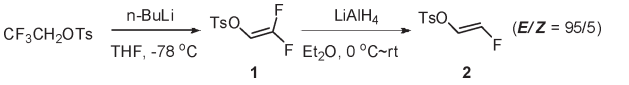
The preparation of vinyl fluorides has inspired many innovative synthetic approaches. In particular, terminal fluorides can be accessed by elimination,[6] electrophilic fluorination,[7] Julia−Kocienski olefination,[8] and Peterson olefination.[9] However, in these approaches, the poor tolerance of functional groups, low stereoselectivity, and moderate to low yields often hinder their applications. Although the Horner−Wadsworth−Emmons reaction[3,10] has been considered as the most successful protocol for the preparation of vinyl fluorides, the starting material halofluorocarbons for the synthesis of fluoromethyl phosphorane ylides have been restricted in use by the law due to their ozone depletion and greenhouse effects.[11] Therefore, the development of a practical and efficient method to synthesize terminal vinyl fluorides is still highly demanding. Herein, we wish to present 2-fluorovinyl tosylate as a useful synthon in the preparation of vinyl fluorides via a Suzuki−Miyaura coupling reaction.

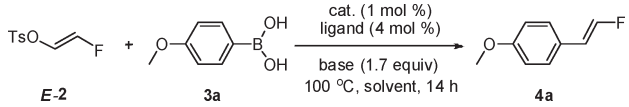
Vinyl tosylates have been found useful in cross-coupling reactions because they can be readily prepared and possess good stability in water.[12] In 2007, Skrydstrup and coworkers reported that 2,2-difluorovinylstyrenes could be successfully synthesized via the Pd-catalyzed Suzuki−Miyaura coupling reaction of 2,2-difluorovinyl tosylate with aryl boronic acids.[13] This method provides a facile and straightforward approach to introduce a *gem*-difluorovinyl substituent onto aromatic compounds. Very recently, Jeong and co-workers reported that 2,2-diaryl-1,1-difluoroethenes could be obtained through the coupling of 2,2-difluoro-1-phenylethenyl tosylate with arylstannane.[14] Nevertheless, few reports could be found in the literature about the synthesis of terminal vinyl monofluorides through a metal-mediated cross-coupling reaction.

Scheme 1. Preparation of 2-Fluorovinyl Tosylate (**2**)



To obtain a variety of vinyl fluorides, 2-fluorovinyl tosylates ***E*-2** and ***Z*-2** were prepared by treating **1** with $LiAlH_4$[15] in ether (Scheme 1). 2,2-Difluorovinyl tosylate (**1**) could be conveniently synthesized from the elimination reaction of 2,2,2-trifluoroethyl tosylate with butyllithium as reported by Skrydstrup.[13] The molar ratio of ***E*-2** and ***Z*-2** in this reaction was 95/5 which was determined by ^{19}F NMR. Two stereoisomers were readily separated by flash column chromatography. Their configurations were confirmed by ^{1}H and ^{19}F NMR.[16]

Table 1. Optimization of the Suzuki−Miyaura Reaction between ***E*-2** and 4-Methoxybenzeneboronic Acid[a]



entry	catalyst	ligand	base[b]	solvent[c]	yield%
1[d]	$Pd(PPh_3)_4$	–	K_3PO_4	Dioxane/H_2O	49
2	$Pd_2dba_3\cdot CHCl_3$	–	K_3PO_4	Dioxane/H_2O	trace
3	$Pd_2dba_3\cdot CHCl_3$	$PBu^n{}_3$	K_3PO_4	Dioxane/H_2O	trace
4	$Pd_2dba_3\cdot CHCl_3$	P(*t*-Bu)$_3$	K_3PO_4	Dioxane/H_2O	trace
5	$Pd_2dba_3\cdot CHCl_3$	PPh_3	K_3PO_4	Dioxane/H_2O	71
6	$Pd_2dba_3\cdot CHCl_3$	dppp	K_3PO_4	Dioxane/H_2O	44
7	$Pd_2dba_3\cdot CHCl_3$	dppb	K_3PO_4	Dioxane/H_2O	70
8	$Pd_2dba_3\cdot CHCl_3$	PCy_3	K_3PO_4	Dioxane/H_2O	98
9	$Pd_2dba_3\cdot CHCl_3$	PCy_3	Na_2CO_3	Dioxane/H_2O	66
10	$Pd_2dba_3\cdot CHCl_3$	PCy_3	K_2CO_3	Dioxane/H_2O	66
11[d]	$Pd(OAc)_2$	PCy_3	K_3PO_4	Dioxane/H_2O	98
12[d]	$PdCl_2(PPh_3)_2$	PCy_3	K_3PO_4	Dioxane/H_2O	94
13	$Pd_2dba_3\cdot CHCl_3$	PCy_3	K_3PO_4	Toluene	49
14	$Pd_2dba_3\cdot CHCl_3$	PCy_3	K_3PO_4	Dioxane	10
15	$Pd_2dba_3\cdot CHCl_3$	PCy_3	K_3PO_4	Toluene	6

[a] ***E*-2** (0.5 mmol) and **3a** (0.55 mmol) were used; yield was determined by ^{19}F NMR using trifluoromethylbenzene as internal standard. [b] Bases were dissolved in water before use except for entries 14 and 15. [c] The volume ratio of Dioxane/H_2O was 3/1, and 2 mL of organic solvent was used. [d] The catalyst loading was 2 mol %.

With ***E*-2** in hand, the optimization of the reaction between ***E*-2** and 4-methoxybenzeneboronic acid was undertaken, and the results are shown in Table 1. The ligands played an important role in the coupling reaction. When $Pd(PPh_3)_4$ was used, the desired product ***E*-**(2-fluorovinyl)-4-methoxybenzene (**4a**) was obtained in 49% yield (entry 1). Only a trace of the desired product was detected by ^{19}F NMR when $Pd_2dba_3\cdot CHCl_3$ was employed (entry 2). Although the yield was low, only the ***E*-**isomer was detected by ^{19}F NMR. When phosphine ligands were added in the coupling reaction, higher yields of the desired product were

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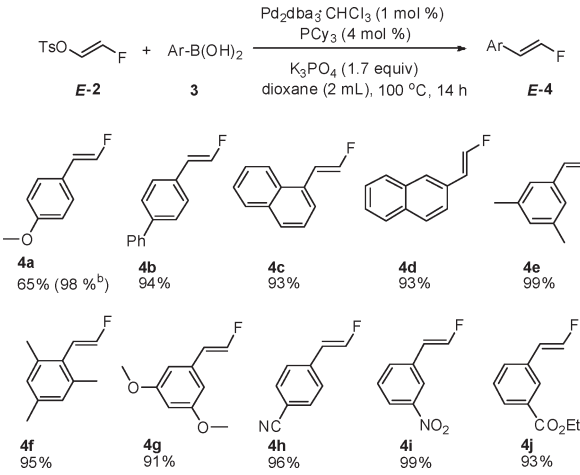
(16) See Supporting Information for details.

obtained (entries 3−8), indicating that extra ligands may improve the efficiency of the catalysis. Among P(*n*-Bu)$_3$, P(*t*-Bu)$_3$, PPh_3, dppp, dppb, and PCy_3 ligands used with $Pd_2dba_3 \cdot CHCl_3$, PCy_3 was proved to be the most efficient candidate in this reaction (entry 8). The screening of precatalysts such as $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ afforded similar results (entries 11 and 12 vs entry 8). In addition, base was also influential (entries 8−10). Potassium phosphate was found to be the optimal base. Therefore, the optimal reaction conditions were identified as follows: 1 equiv of ***E*-2**, 1.1 equiv of arylboronic acids in the presence of 1 mol % $Pd_2dba_3 \cdot CHCl_3$, 4 mol % PCy_3, and 1.7 equiv potassium phosphate in dioxane and H_2O at 100 °C for 14 h.

Table 2. Substrate Scope of the Suzuki−Miyaura Reaction between ***E*-2** and Arylboronic Acids[a]



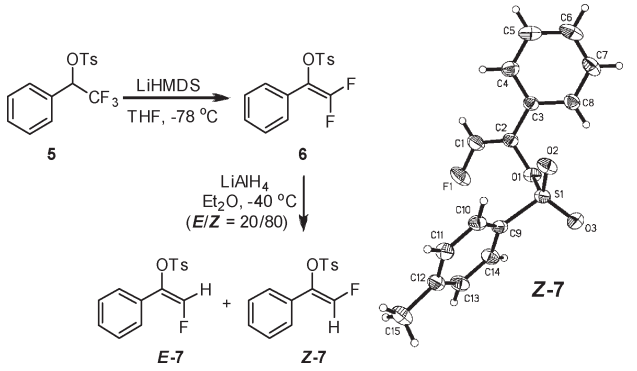
[a] Isolated yield; **5a** (0.5 mmol) and boronic acid (0.55 mmol) were used. [b] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

This procedure was then extended to other arylboronic acids, and the results are shown in Table 2. The functional group tolerance was quite broad. Substrates bearing electron-withdrawing groups, electron-donating groups, and highly steric substituents can be successfully coupled with vinylfluoride tosylate in excellent yields. All of the products are the ***E*** isomer, indicating that the configuration was completely retained in the reaction.

When our work was in progress, Paquin and co-workers reported the first synthesis of 1,1-diaryl-2-fluoroethenes using Suzuki−Miyaura cross-coupling via boronic acids and vinylbromides.[17] Enlightened by his work to expand the scope and applicability of our method, 2-fluoro-1-phenylvinyl tosylate (**7**) was synthesized and then converted to 1,1-diaryl vinylfluorides (**8**) under the optimized reaction conditions. Since **6** and **7** are more susceptible to nucleophilic attack, LiHMDS was chosen for deprotonation and elimination of 2,2,2-trifluoro-1-phenylethyl tosylate (**5**) at −78 °C, giving 2,2-difluoro-1-phenylvinyl tosylate (**6**)

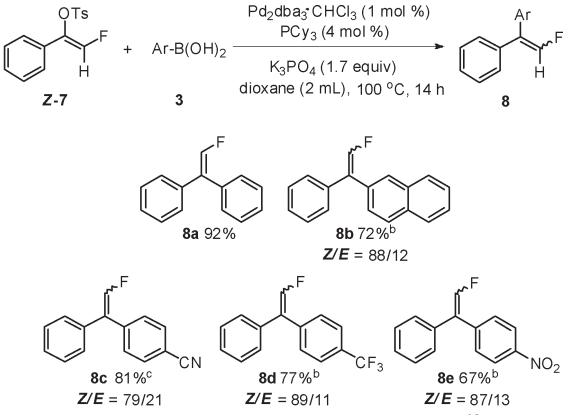
(17) Landelle, G.; Turcotte-Savard, M.-O.; Marterer, J.; Champagne, P. A.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 5406–5409.

Scheme 2. Preparation of the 2-Fluoro-1-phenylvinyl Tosylate (**7**)



in 80% yield, and subsequent treatment with $LiAlH_4$ at −40 °C afforded ***Z*-7** and ***E*-7** in moderate yields, which could be separated by flash column chromatography (Scheme 2). The configuration of the major isomer ***Z*-7** was confirmed by single crystal X-ray diffraction analysis.[18]

Scheme 3. Coupling Reaction between ***Z*-7** and Boronic Acids[a]



[a] Isolated yield and the *E*/*Z* selectivity were determined by ^{19}F NMR of the reaction mixture. [b] Isolated as a ***E*/*Z*** mixture. [c] The ***E*/*Z*** isomers were separated by flash column chromatography.

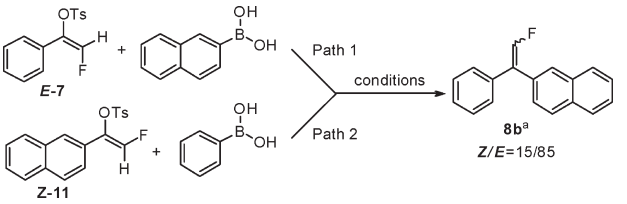
As shown in Scheme 3, ***Z*-7** showed good reactivity for the coupling reaction to afford the corresponding 1,1-diaryl fluorides. 2-Fluoro-1,1-diphenylethene (**8a**) was successfully obtained in 92% isolated yield. While the unsymmetrically substituted diaryl vinylfluorides **8b**−**e** were synthesized in moderate stereoselectivity. Two stereoisomers of **8c** could be readily separated by column chromatography, and the configuration was assigned by H,H-NOESY.[19]

With the treatment of ***E*-7** with naphthalen-2-ylboronic acid under optimal conditions (Scheme 4), compound **8b** was obtained in 95% yield with a 15/85 *Z*/*E* selectivity.

(18) CCDC 797215 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) See Supporting Information for details.

Scheme 4. Synthesis of **8b** from ***Z*-11** and ***E*-7**[a]



[a] 95% yield of **8b** was obtained from ***E*-7** and 91% yield was obtained from ***Z*-11**.

A similar result was also found in the reaction of ***Z*-11** with phenylboronic acid.[20] It seems that the configuration of the C=C bond was almost maintained in this reaction.

It is interesting to note that the reduction of difluoroalkenes **1** and **6** with $LiAlH_4$ preferentially resulted in ***E*-2** and ***Z*-7** isomers, respectively. This reaction may proceed through an addition−elimination pathway (Scheme 5). In this process, the coordination of atomic Li with fluoride would make the fluoride more prone to leave than tosylate. Moreover, the steric repulsion between the OTs group and F makes TS2 more favorable and ***E*-2** was thus isolated as a major isomer. For compound **6**, the introduction of a phenyl ring would make the carbanion tend to adopt sp^2 hybridization[21] in **6′** due to the better electron conjugated effect between the phenyl ring and the negative charge. Therefore, the steric repulsion between Ph and F may destabilize TS4 and the corresponding product ***E*-7** was less abundant. The ratio of ***Z*/*E*** is thus inversed from 5/95 in **2** to 80/20 in **7**.

In the presence of $Pd_2dba_3 \cdot CHCl_3/PCy_3/K_3PO_4$ at 100 °C for 14 h, ***Z*-8c** could isomerize to ***E*-8c**, giving a mixture of ***Z*/*E*** (62/38). While the starting material ***Z*-7** was employed, no isomerization happened.[22] This indicates that the stereoselectivity observed in the coupling reaction was probably attributed to the product isomerization under the optimized Suzuki−Miyaura reaction conditions.

(20) See Supporting Information for details.

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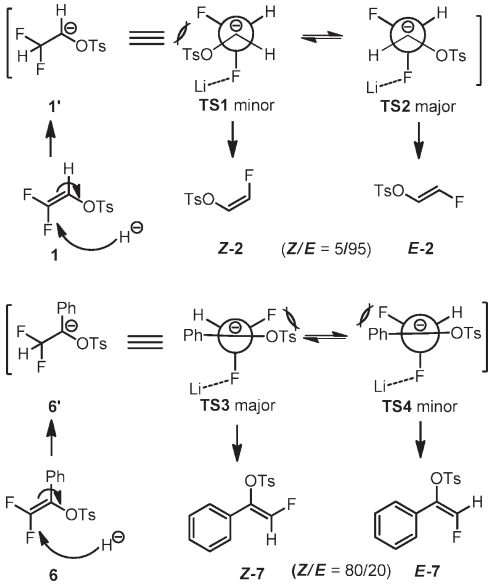
(22) See Supporting Information for details.

Scheme 5. Proposed Mechanism for the Stereoselectivity of Monofluoroalkenes



In conclusion, 2-fluorovinyl tosylate and 2-fluoro-1-phenylvinyl tosylate were synthesized and employed to prepare 1-aryl vinyl fluorides and 1,1-diaryl vinyl fluorides. High yields and good stereoselectivity were achieved in the reaction of ***E*-2** with aryl boronic acids. Further studies on the synthesis of 1,2-diaryl-fluorovinyls are underway in our laboratory.

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Supporting Information Available. Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.