Alkenyl Fluorosulfates – Expedient Partners for Palladium-Catalyzed Cross-Coupling Reactions

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Abstract

Alkenyl fluorosulfates are evaluated as the partners of palladium-catalyzed cross-coupling reactions and alternative to more common triflates and halides. Efficient protocols for the multigram synthesis of title reactants using reaction of carbonyl compounds with SO_2F_2 were documented. Reactivity of alkenyl fluorosulfates in Suzuki, Sonogashira, Heck, Stille, and Buchwald-Hartwig reactions, as well as Miyaura borylation under typical conditions was studied, and limitations of the methods were established. It was found that alkenyl flurosulfates have similar or even higher reactivity in the cross-coupling reactions as compared to alkenyl triflates.

Introduction

It is hard to imagine any other chemical transformation that changed the landscape of modern synthetic chemistry as much as palladium-catalyzed cross-coupling reactions did. Recognized with Nobel Prize in 2010, the advancements in this field made by Suzuki, Negishi, Heck, and others several decades ago now became everyday tools in the chemistry labs.[1] A major part of efforts was put into extending the scope of nucleophilic components of the cross-coupling reactions, with prominent examples of saturated boronates,[2] trifluoroborates,[3] MIDA boronates,[4,5] stannatranes,[6] heteroatom nucleophiles,[7,8] and many other outstanding developments.[9] The scope of electrophilic partners was typically considered self-explanatory. In the case of aromatic series, it typically included various (het)aryl halides, sometimes – triflates and other sulfonates (Fig. 1).[10] For aliphatic counterparts, alkenyl halides are also common but the corresponding triflates (easily obtained through enolization of carbonyl compounds) are used more often.

While alkenyl triflates are reactive and versatile substrates for cross-coupling reactions, they have several drawbacks. Firstly, generation of alkenyl triflates involves the use of triflating agents like $PhNTf_2$, Tf_2O, or Comin's reagent,[11] which complicates their isolation in pure form, and (typically) strong bases, which may limit functional group compatibility. Secondly, trifluoromethanesulfonate is produced as a by-product of the cross-coupling step, which reduces its atom economy and can raise environmental concerns.[12]

In 1991, Roth and Fuller suggested aryl fluorosulfates as a possible alternative to aryl triflates in the cross-coupling reactions.[13] Since then, these compounds have been widely exploited for that purpose.[14–16] On the contrary, alkenyl fluorosulfates received virtually no attention in this regard.[17–20] Meanwhile, alkenyl fluorosulfates **1** can be easily prepared by the reaction of carbonyl compounds **2** and SO_2F_2 in the presence of a relatively mild base (Scheme 1).[19–21] Due to that, this process can benefit from high functional group compatibility of the whole strategy, apart from consuming SO_2F_2 which has been named among potent greenhouse gases.[22]

In this work, we present our results on the multigram preparation of alkenyl fluorosulfates **1** and their thorough exploration as the electrophilic partners in the palladium-catalyzed cross-coupling reactions. The scope of the covered transformations includes Suzuki, Sonogashira, Heck, Stille, and Buchwald-Hartwig reactions, as well as Miyaura borylation.

Results and Discussion

We have started our work with the exploration of a wide range of carbonyl compounds **2a–t** in the reaction with SO_2F_2 (Scheme 1). Among the reported protocols for this transformation, we initially have turned our attention to the method of Leroux and co-authors using DBU as the base and CH_2Cl_2 as the solvent;[19,21] other variations involving *t*BuOK, LDA, or LiHMDS[20,21] were less promising. The reaction was performed at rt (20 °C) using a two-fold excess of DBU (protocol *A*). It was found that the method tolerated ketal (**1b**), *N*-Boc-protected amine (**1c** and **1i**), ester (**1d** and **1e**), *gem*-CF_2 (**1f**), and alkene (**1g**) moieties, was compatible with α-tetralone (product **1h**) as the substrate. With aldehyde **2j** and β-keto esters **2l** and **2m** a 1.1-fold excess of the base was used to decrease potential side reactions (protocol *B*). In the case of β-diketone **2k** and β-keto nitrile **2n**, ethyl diisopropyl amine (1.1 eq) was used as the base instead of DBU (protocol *C*), which diminished decomposition of the products significantly.

Limitations of the method included aldehydes and ketones containing small rings (**2o–q**) and acyclic ketones (**2r**), which have complex mixtures of unidentified products under any of the above protocols. Imide **2s** did not react with SO_2F_2 in the presence of either DBU or *i*Pr_2NEt. Piperidine derivative **2t** did not work as well; no reaction occurred in the presence of *i*Pr_2NEt (protocol *C*), and complex mixtures of products were obtained following protocols *A* or *B*.

Notably, all compounds **1a–n** demonstrated considerable stability towards on-the-shelf storage: they remained unchanged at rt for at least six months.

Next, a typical protocol for the Suzuki reaction of alkenyl triflates ($Pd(PPh_3)_4$ (0.1 eq), K_3PO_4 (1.5 eq), 1,4-dioxane) originally published by Suzuki and co-authors[23] was applied to an equimolar mixture of fluorosulfate **1i** and boronic acid **3a** (Scheme 2). Variation of the reaction temperature in the range of 20–80 °C showed that the highest yield of product **4ia** (according to ^{1}H NMR spectra) was observed at 40 °C. The applicability of the protocol was checked for a wider range of fluorosulfates **1a–i** and (het)aryl boronic acids **4a–i**. Corresponding products **4ac–ib** were obtained in 50–85% yields. The method did not work with fluorosulfate **1n**. A complex mixture was obtained in this case, likely due to polymerization at some step.

Sonogashira reaction of alkenyl fluorosulfates **1a–n** and various terminal alkynes **5** was another cross-coupling that worked well with wide range of substrates. Again, one of the common protocols was used in this case – alkyne **5** (1.05 eq), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.05 eq), CuI (0.1 eq), Et_3N (5 eq), THF, rt.[24] Corresponding enynes **6ac**–**na'** were obtained in 75–87% yield (Scheme 3). Notably, the method was compatible with flurosulfate **1n**. With trimethylsilyl acetylene (**5a**), the products of *C*-desilylation (**6ba'**,

6ca', and **6na'**) were isolated in some cases after the HPLC purification. Limitation of the method included electron-poor alkynes such as ethyl propiolate (**5f**), likely due to polymerization processes.

Heck reaction of fluorosulfates **1a–n** and monosubstituted alkenes **7** followed a protocol described by Stille and co-authors for alkenyl triflates ($Pd(PPh_3)_2Cl_2$ (0.05 eq), Et_3N (3 eq), DMF) (Scheme 4).[25] Variation of the reaction temperature for substrates showed that 60 °C were optimal to achieve good conversion of the starting materials and avoid excessive product polymerization. The method worked well with ethyl acrylate (**7a**), so that products **8ba–da** were isolated in 77–83% yield. Neither variation worked non-activated alkenes **7f–i**. In the case of fluorosulfate **1n**, product **8na** was detected by ^{1}H NMR spectroscopy in 36% yield but could not be isolated in pure form.

Stille coupling of alkenyl triflates **1a–i** with heteroaromatic tris(*n*-butyl)stannanes **9** was performed in the presence of $Pd(PPh_3)_2Cl_2$ (0.05 eq) – CuI (0.2 eq) as the catalytic system in refluxing THF as the solvent (Scheme 5).[26,27] Cross-coupling products **10ba–ia** were obtained in 87–93% yield. This protocol was not compatible with aliphatic stannanes **9e–h**; in all cases, complex mixtures of unidentified products were obtained instead of target dienes.

Miyaura borylation of alkenyl fluorosulfates **1a–i** with B_2Pin_2 involving the use of $Pd(PPh_3)_2Cl_2{\cdot}2PPh_3$ as a catalyst, PhOK as a base, and toluene as a solvent at 50°C[28,29] enabled full conversion of starting materials and gave target boropinacolates **11a–i** in 70–95% yield (Scheme 6).

Buchwald-Hartwig amination of alkenyl fluorosulfates **1a–n** was most challenging, partially due to the limited stability of the corresponding products. After some preliminary experiments with substrate **1a** and benzophenone imine (**12a**) as the *N*-nucleophile, we have found that using a combination of $Pd(OAc)_2$ (3 mol%) and $Pd_2(dba)_3$ (3 mol%), XantPhos (10 mol%) as a ligand, Cs_2CO_3 (1.4 eq) as a base, and 1,4-dioxane as a solvent at 50°C was optimal. Both $Pd(OAc)_2$ and $Pd_2(dba)_3$ were much less efficient when used individually. Other variations including BINAP as the ligand and *t*BuOK as the base were not fruitful either. An alternative protocol that gave comparable results involved the use of XantPhos Pd G3 (5 mol%) and Cs_2CO_3 (1.4 eq) in toluene at 80°C. However, the process was complicated by partial product decomposition because of the higher reaction temperature.

These optimized reaction conditions worked well for the amination of various alkenyl fluorosulfates **1a–n**, so that corresponding imines **13aa**–**na** could be isolated in 73–94% yield (Scheme 7). The reaction also worked well with pivaloyl amide (**12c**) (91% yield of **13ac**). In the case of *N*-methylaniline (**12b**), aniline (**12e**), and 3-aminopyridine (**12f**), corresponding enamine **13ib** or imines **13ea** and **13fa** were formed in 67–70% yield according to ^{1}H NMR spectra, but we could not isolate them in pure form due to the hydrolytic lability. Further limitations of the method included aliphatic amines (likely due to side reactions at the sulfur atom) and heteroaromatic amines with low nucleophilicity (that did not react at all or gave complex mixtures upon elevated temperatures).

Finally, fluorosulfate **1i** and corresponding triflate **14** were evaluated in Suzuki, Sonogashira, and Stille reactions, as well as Miyaura borylation under the optimized conditions described above (Table 1). It was found that compound **1i** demonstrated similar or higher product yields as compared to **14** according to ^{1}H NMR spectra. These data show that fluorosulfates can be indeed considered a very good alternative to triflates in terms of their reactivity towards the cross-coupling reactions.

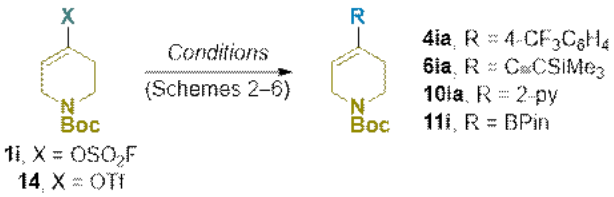
Conclusions

Alkenyl fluorosulfates are readily accessible and convenient yet underexplored components for various palladium-catalyzed cross-coupling reactions that can become a valuable alternative to commonly used alkenyl triflates. The title compounds can be easily obtained by mild base-promoted reaction of carbonyl compounds and sulfuryl fluoride. They are stable towards storage and produce only inorganic by-products after the cross-coupling. The utility of alkenyl fluorosulfates was demonstrated for the typical protocols of Suzuki, Sonogashira, Heck, Stille, and Buchwald-Hartwig reactions, as well as Miyaura borylation. The limitations of the developed methods were related to the limited stability of the products or low reactivity of the second reaction partners. The reactivity of alkenyl fluorosulfates themselves was similar or superior to that of the corresponding alkenyl triflates in model experiments.

Experimental Section

The solvents were purified according to the standard procedures.[30] All starting materials were obtained from Enamine Ltd. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. Reverse-phase HPLC purification was performed using XBridge C18 (100 × 19mm, 5 μm) or Chromatorex 18 SMB100-5T (100 × 19mm, 5 μm) columns with H_2O/MeOH or H_2O/CH_3CN gradient elution. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR, and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in pp (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$,

Table 1
Cross-coupling reactions of substrates **1i** and **14**.



#	Reaction	Scheme[a]	Coupling partner	Product	Yield (%),[b] starting from	
					1i	**14**
1	*Suzuki*	2	4-$CF_3C_6H_4B(OH)_2$ (**3a**)	**4ia**	80	40
2	*Sonogashira*	3	TMSC≡CH (**5a**)	**6ia**	93	63
3	*Stille*	5	(2-py)$SnBu_3$ (**9a**)	**10ia**	86	80
4	*Miyaura*	6	B_2Pin_2	**11i**	77	81

[a] Reactions were performed under the conditions shown in Schemes 2–6.
[b] Yields according to ^{1}H NMR spectra; *m*-xylene was used as an internal standard for the integration. 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 MS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General procedure for the synthesis of alkenyl fluorosulfates 1. To a solution of carbonyl compound **2** (0.1 mol) in CH_2Cl_2 (200 mL) DBU (29.9 mL, 0.2 mol, 2 eq) (*Method* **A**), or DBU (16.4 mL, 0.11 mol, 1.1 eq) (*Method* **B**), or *i*Pr_2NEt (18.7 mL, 0.11 mol, 1.1 eq) (*Method* **C**) was added dropwise at rt, and the resulting mixture was stirred for 15 min. Then, the reactor was vacuumed, and a 5-L balloon filled with SO_2F_2 was connected through a septum. The reaction mixture was stirred at rt for 12 h. Then, the balloon was disconnected, and the reaction mixture was poured into 1 M aq $NaHSO_4$ (200 mL). The organic phase was separated, washed with 1 M aq $NaHSO_4$ (70 mL), brine (70 mL), dried over Na_2SO_4. The residue was triturated in hexanes, hexanes – EtOAc (19:1), or hexanes – EtOAc (9:1) (100 mL). Activated charcoal (10 g) was added, and the mixture was stirred for 10 min, then filtered through a silica gel pad. The combined filtrates were evaporated in vacuo to give pure product **1**.

General procedure for the Suzuki reaction of alkenyl fluorosulfates 1. To a solution of alkenyl fluorosulfate **1** (0.01 mol, 1 eq) in 1,4-dioxane (20 mL), boronic acid **3** (0.01 mol, 1 eq) and K_3PO_4 (3.18 g,

0.015 mol, 1.5 eq) were added. Then, argon was passed through the reaction mixture upon stirring for 5 min. $Pd(PPh_3)_4$ (1.16 g, 1 mmol, 10 mol%) was added, and argon was passed through the reaction mixture upon stirring for additional 5 min. The resulting mixture was stirred at 40 °C for 16 h, then cooled. The precipitate was filtered off, the combined filtrates were evaporated in vacuo, and the residue was purified by preparative HPLC to give product **4**.

General procedure for the Sonogashira reaction of alkenyl fluorosulfates 1. To a solution of alkenyl fluorosulfate **1** (0.01 mol, 1 eq) in THF (20 mL), alkyne **5** (0.0105 mol, 1.05 eq), Et_3N (6.97 mL, 0.05 mol, 5 eq), and CuI (0.190 g, 1 mmol, 10 mol%) were added. Then, argon was passed through the reaction mixture upon stirring for 5 min. $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.408 g, 0.5 mmol, 5 mol%) was added, and argon was passed through the reaction mixture upon stirring for additional 5 min. The resulting mixture was stirred at rt for 16 h. The precipitate was filtered off, the combined filtrates were evaporated in vacuo, and the residue was purified by preparative HPLC to give product **6**.

General procedure for the Heck reaction of alkenyl fluorosulfates 1. To a solution of alkenyl fluorosulfate **1** (0.01 mol, 1 eq) in DMF (20 mL), alkene **7** (0.02 mol, 2 eq), and Et_3N (4.18 mL, 0.03 mol, 3 eq) were added. Then, argon was passed through the reaction mixture upon stirring for 5 min. $Pd(PPh_3)_2Cl_2$ (0.351 g, 0.5 mmol, 5 mol%) was added, and argon was passed through the reaction mixture upon stirring for additional 5 min. The resulting mixture was stirred at 70 °C for 16 h, then cooled. The precipitate was filtered off, the combined filtrates were evaporated in vacuo, and the residue was purified by preparative HPLC to give product **8**.

General procedure for the Stille reaction of alkenyl fluorosulfates 1. To a solution of alkenyl fluorosulfate **1** (0.01 mol, 1 eq) in THF (20 mL), stannane **9** (0.012 mol, 1.2 eq) and CuI (0.952 g, 5 mmol, 0.2 eq) were added. Then, argon was passed through the reaction mixture upon stirring for 5 min. $Pd(PPh_3)_2Cl_2$ (0.351 g, 0.5 mmol, 5 mol%) was added, and argon was passed through the reaction mixture upon stirring for additional 5 min. The resulting mixture was refluxed upon stirring for 16 h, then cooled. MeOH (2 mL) and CsF (3.04 g, 0.02 mol, 2 eq) were added, the resulting mixture was stirred at 40 °C for 3 h and then cooled. The precipitate was filtered off, the combined filtrates were evaporated in vacuo, and the residue was purified by preparative HPLC to give product **10**.

General procedure for the Miyaura borylation of alkenyl fluorosulfates 1. To a solution of alkenyl fluorosulfate **1** (0.01 mol, 1 eq) in toluene (20 mL), B_2Pin_2 (3.81 g, 0.015 mol, 1.5 eq), PhOK (1.98 g, 0.015 mol, 1.5 eq), and PPh_3 (1.31 g, 5 mmol, 0.2 eq) were added. Then, argon was passed through the reaction mixture upon stirring for 5 min. $Pd(PPh_3)_2Cl_2$ (0.702 g, 1 mmol, 10 mol%) was added, and argon was passed through the reaction mixture upon stirring for additional 5 min. The resulting mixture was stirred at 50 °C for 16 h, then cooled. The precipitate was filtered off, the combined filtrates were evaporated in vacuo, and the residue was purified by preparative HPLC to give product **11**.

General procedure for the Buchwald-Hartwig reaction of alkenyl fluorosulfates 1. To a solution of alkenyl fluorosulfate **1** (0.01 mol, 1 eq) in dioxane (20 mL), amine **12** (0.012 mol, 1.2 eq), XantPhos (0.58 g, 1

mmol, 0.1 eq) and Cs_2CO_3 (3.59 g, 0.014 mol, 1.4 eq) were added. Then, argon was passed through the reaction mixture upon stirring for 5 min. $Pd(OAc)_2$ (0.067 g, 0.3 mmol, 3 mol%) and $Pd_2(dba)_3$ (0.274 g, 0.3 mmol, 3 mol%) were added, and argon was passed through the reaction mixture upon stirring for additional 5 min. The resulting mixture was stirred at 50 °C for 16 h, then cooled. The precipitate was filtered off, the combined filtrates were evaporated in vacuo, and the residue was purified by preparative HPLC to give product **13**.

Declarations

Supporting Information

The authors have provided compound characterization data and copies of NMR spectra in the Supporting Information File.

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Conflict of Interests

The authors are employees of Enamine Ltd. offering the building blocks and products described in this paper in the company's catalog.

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Schemes

Schemes 1 to 7 are available in the Supplementary Files section

Figures

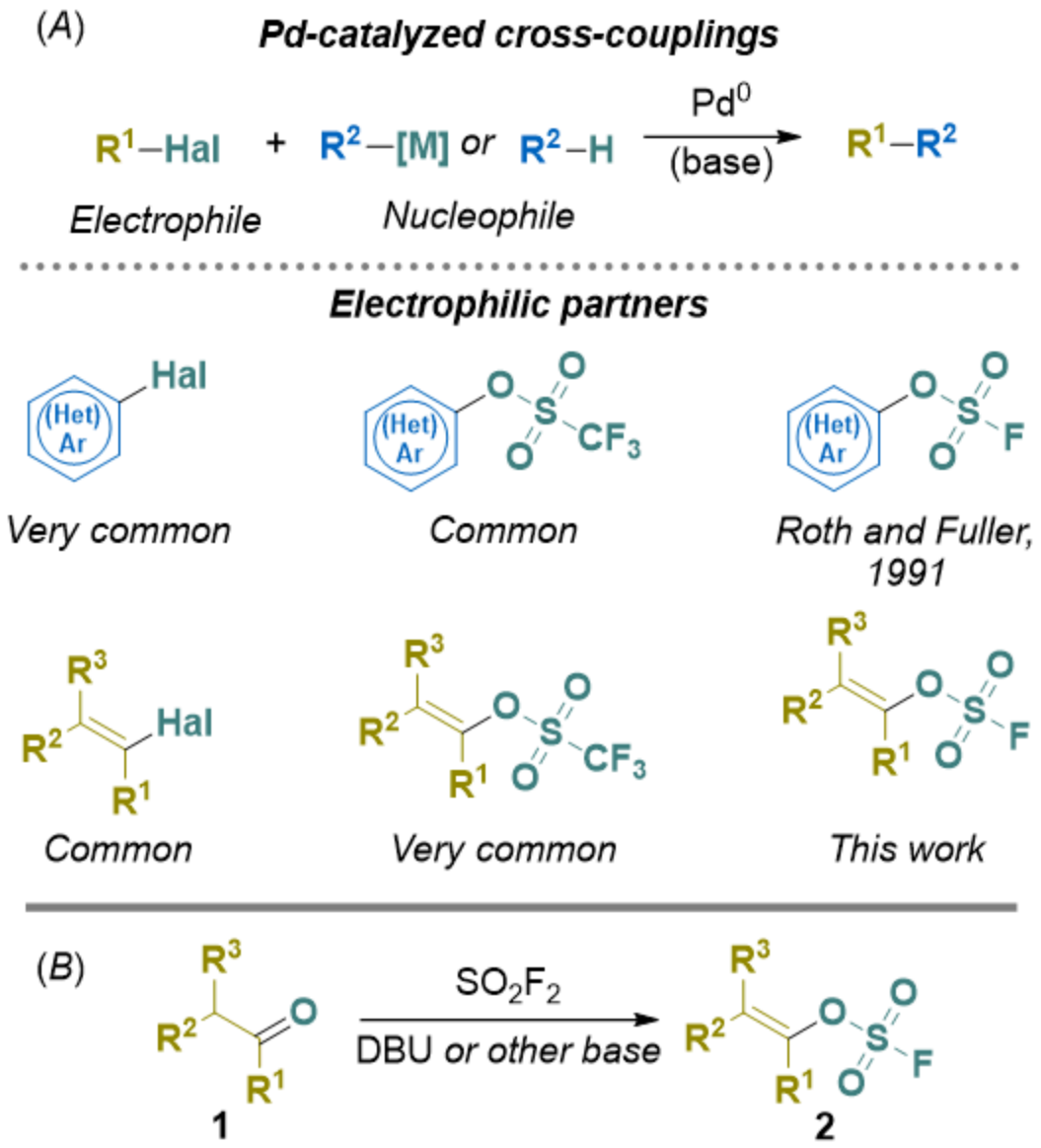

Figure 1

(*A*) Electrophilic partners for palladium-catalyzed cross-coupling reactions. (B) Preparation of alkenyl fluorosulfates.

Supplementary Files

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