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Palladium-Catalyzed, Ligand-Free Suzuki Reaction in Water Using Aryl Fluorosulfates

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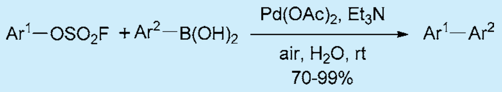
Supporting Information



$$Ar^1{-}OSO_2F + Ar^2{-}B(OH)_2 \xrightarrow[\text{air, H}_2\text{O, rt; 70-99\%}]{\text{Pd(OAc)}_2\text{, Et}_3\text{N}} Ar^1{-}Ar^2$$

ABSTRACT: Aryl fluorosulfates were prepared by a simple method and employed as coupling partners in the Suzuki−Miyaura reaction. The cross-coupling reactions were performed in water under air at room temperature without ligands or additives such as surfactants or phase-transfer reagents and proceeded smoothly to give excellent yields. Aryl fluorosulfates could also be used as alternatives to halides or triflates in other coupling reactions.

Aryl, heteroaromatic, and vinyl halides are broadly used as electrophilic partners for transition-metal-catalyzed cross-coupling reactions. Unfortunately, their environmental toxicity and high costs are obstacles to large-scale syntheses in industrial applications. Much attention has been paid to phenol- and enol-derived electrophiles,[1] which are more easily accessible.[2] However, the C−O bond dissociation energies of esters, carbamates, carboxylates, and even ethers[3] are relatively high.[4] Although traditional sulfates such as triflates (OTf),[5] mesylates (OMs).[6] and tosylates (OTs)[7] have been widely used, they are expensive and exhibit low reactivity.

Historically, fluorosulfates have long been known as "super sulfates" with the ability to participate in transition-metal-catalyzed coupling reactions. The use of fluorosulfates as the electrophilic components in Negishi and Stille cross-couplings[8] and palladium-catalyzed alkoxy carbonylation reactions[9] was originally investigated by the process group at Bristol-Myers Squibb. In general, aryl fluorosulfates were prepared from phenols and fluorosulfonic acid anhydride, but the process involved handling dangerous strong acid anhydrides and generated a large volume of waste.[10] Therefore, no reliable methods are available for the preparation of fluorosulfates, and their chemistry remains largely unexplored. The Sharpless group reported a simple method to prepare aryl fluorosulfates from phenols and sulfuryl fluoride in the presence of triethylamine in 2014.[11] The fumigant sulfuryl fluoride (SF) is currently used as an alternative to methyl bromide for the disinfestation of buildings and postharvest commodities. The SF is produced on an industrial scale; the global annual production of SF is estimated to be approximately 3 million kilograms since 2000.[12] The SF has low toxicity and is relatively cheap ($1/kg, MAUI (Hangzhou) Electronic Chemicals Co., Ltd.). Our group aimed to evaluate the application of fluorosulfates as an alternative to triflates in transition-metal-catalyzed cross-coupling reactions. Of the various coupling reactions, the Suzuki reaction is one of the most powerful and convenient approaches for C−C bond formation. Over the past several years, numerous efforts have been made to develop a green, ligand-free catalytic system for the Suzuki cross-coupling reaction for large-scale industrial applications. Examples of these efforts include PdCl$_2$ in *i*-PrOH/H$_2$O,[13] PdCl$_2$ in DMF/H$_2$O,[14] Pd(OAc)$_2$ in Pd/C in aqueous alcohol,[15,16] and Pd(OAc)$_2$ in aqueous acetone.[17] In the above-mentioned work, however, large amounts of organic solvents were required to dissolve the substrates. Utilizing phase-transfer complexes such as PEG is also a common strategy for performing the reaction without ligands in water.[18] Although it has been reported that the Suzuki−Miyaura reaction can be performed in neat water,[19] harsh conditions are often mandatory. In this paper, we report a simple and efficient catalytic system for the Suzuki−Miyaura cross-coupling reaction of fluorosulfates in an aqueous solution under air without any additives. This system gave the desired products in good to excellent yields, and a wide range of functional groups could be used.

A series of aryl fluorosulfates were synthesized from phenols and sulfuryl fluoride in the presence of triethylamine in moderate to excellent yields (75−99%) (Scheme 1). Sigma−Aldrich has now commercialized these aryl fluorosulfates using the same synthetic method, and the product numbers are listed in Scheme 1.

We first compared a variety of coupling partners, including aryl fluorosulfates, halides, and other traditional leaving groups, for boronic acids in the Suzuki−Miyaura reaction (Table 1).[20] The aryl chloride and arylboronic acid hardly reacted in this simple catalytic system (in pure water under air atmosphere at room temperature in the absence of other additives, using only

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Scheme 1. Preparation of Different Aryl Fluorosulfates

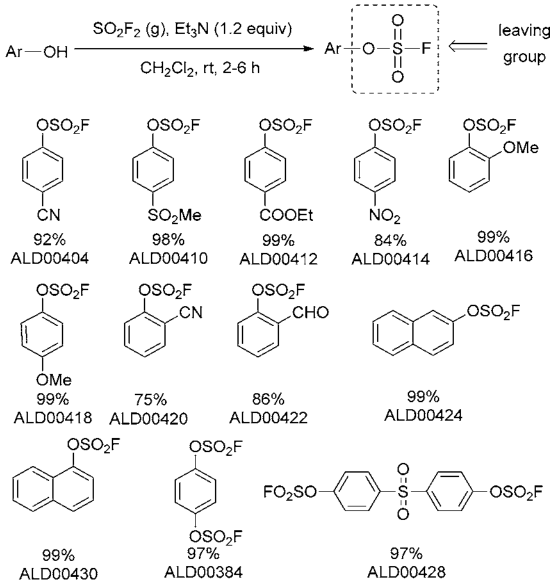
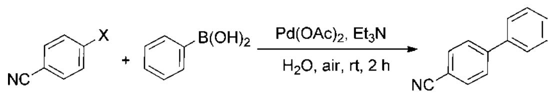


Table 1. Performance of Different Leaving Groups[a]



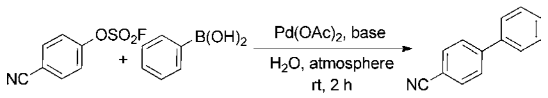
entry	X	yield[b] (%)
1	Cl	trace
2	OTs	0
3	OMs	0
4	Br	98
5	I	72
6	OSO_2F	99
7	OTf	99

[a]General conditions: rt, aryl-X (1.0 mmol), arylboronic acid (1.5 mmol), $Pd(OAc)_2$ (1 mol %), Et_3N (3.0 mmol), H_2O (3.0 mL), under air. [b]Isolated yields.

triethylamine (3−5 equiv) as the base and cosolvent) (Table 1, entry 1). As expected, aryl tosylate (Ar-OTs) and aryl mesylate (Ar-OMs) were unreactive, performing even worse than the aryl chloride (Table 1, entries 2 and 3). The aryl bromide was found to react smoothly to give 98% isolated yield (Table 1, entry 4), but the aryl iodide gave only a moderate yield (Table 1, entry 5). The reaction with aryl fluorosulfate was as efficient as the reaction with aryl triflate (Ar-OTf), giving nearly the same yield under the same conditions (Table 1, entries 6 and 7). Thus, aryl fluorosulfates can be used as cheap alternatives to aryl halides and triflates in the Suzuki−Miyaura reaction.

We then examined the effectiveness of different atmosphere and base in the Suzuki cross-coupling reaction. The cross-coupling between 4-cyanophenyl fluorosulfate (1.0 mmol) and phenylboronic acid (1.5 mmol) in the presence of 1 mol % of $Pd(OAc)_2$ in water was chosen as the model reaction. The results are summarized in Table 2. The organic bases resulted in much higher yields (Table 2, entries 4−7) than the inorganic bases (Table 2, entries 1−3). 1,5-Diazabicyclo[4.3.0]non-5-ene, though miscible in water, gave only a trace amount of the product (Table 2, entry 8). Diisopropylamine, which was the most efficient base in Qiu's work,[19a] gave a low isolated yield here (Table 2, entry 9). Compared to the other amines, triethylamine was found to be the most efficient base with 97% isolated yield. Next, we examined the catalytic system under different atmospheres, specifically, pure oxygen and argon. The yield obtained under pure oxygen was slightly higher than that obtained under argon (Table 2, entries 10 and 11). It has been reported that the homocoupling of arylboronic acid was facilitated by the high oxygen level in a pure oxygen atmosphere,[21] while the catalyst deactivation was faster in the absence of O_2 (under argon), leading to a short catalyst life.[22]

Table 2. Optimization of the Reaction Conditions for Suzuki Coupling[a]



entry	base	yield[e] (%)
1	Na_2CO_3	27
2	K_2CO_3	29
3	Cs_2CO_3	30
4[b]	trimethylamine	65
5	triethylamine	97
6	*N*,*N*-diisopropylethylamine	91
7	4-methylmorpholine	93
8	1,5-diazabicyclo[4.3.0]non-5-ene	trace
9	diisopropylamine	31
10[c]	triethylamine	94
11[d]	triethylamine	90

[a]General conditions: rt, 4-cyanophenyl fluorosulfate (1.0 mmol), phenylboronic acid (1.5 mmol), $Pd(OAc)_2$ (1 mol %), base (3.0 mmol), H_2O (3.0 mL), under air atmosphere. [b]TMA (0.6 mL, 33 wt % in aqueous solution), H_2O (2.4 mL). [c]Under oxyen atmosphere. [d]Under argon atmosphere. [e]Isolated yields.

To investigate further the scope and limitations of this methodology, the optimized conditions based on the data in Table 2, entry 5, were used for the reactions between various aryl fluorosulfates and arylboronic acids. The results are given in Table 3. The electron-deficient aryl fluorosulfates showed excellent reactivity, giving high product yields in short reaction times (Table 3, entries 1−3). However, a higher (5 mol %) catalyst loading and longer reaction time were required to obtain satisfactory results when the substrates were electron-rich (Table 3, entries 4, 5, and 13) due to faster catalyst deactivation and slower oxidative addition. We next examined different arylboronic acids containing electron-withdrawing or electron-donating groups. The results illustrated that the electronic properties of the arylboronic acids did not significantly influence the catalytic activity (Table 3, entries 6−8). Other aryl fluorosulfates and arylboronic acids gave the desired biaryls in excellent yields (Table 3, entries 9−11). 2-Cyano-4′-methylbiphenyl, an important hypertensive drug intermediate,[23] could be obtained in 71% yield (Table 3, entry 12). It should be noted that naphthyl-OSO_2F coupled efficiently with arylboronic acids (Table 3, entries 14−16). Interestingly, the catalytic system also showed good reactivity in double Suzuki couplings of diaryl-OSO_2F to afford the corresponding products (Table 3, entries 17 and 18). Finally, using potassium aryltrifluoroborates[24] as alternatives to the boronic acids resulted in moderate to good yields (Table 3, entries 19−21).

To broaden the application of these easily prepared, useful aryl fluorosulfates, we extended their use to other types of coupling reactions, including Heck (Table 4, entry 1),

Table 3. Suzuki–Miyaura Reactions of Aryl Fluorosulfates[a]

$$\mathrm{Ar^1{-}OSO_2F} + \mathrm{Ar^2{-}B(OH)_2} \xrightarrow[\text{air, }\mathrm{H_2O}\text{, rt}]{\mathrm{Pd(OAc)_2,\ Et_3N}} \mathrm{Ar^1{-}Ar^2}$$

entry	Ar^1	Ar^2	time (h)	yield[f] (%)
1	4-$MeO_2SC_6H_4$	Ph	2	93
2	4-$EtOOCC_6H_4$	Ph	2	99
3	4-$O_2NC_6H_4$	Ph	2	96
4[b]	2-$MeOC_6H_4$	Ph	6	94
5[b]	4-$MeOC_6H_4$	Ph	6	90
6	4-NCC_6H_4	4-$MeOC_6H_4$	2	93
7	4-NCC_6H_4	4-FC_6H_4	2	94
8	4-NCC_6H_4	4-$F_3CC_6H_4$	2	91
9	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	2	93
10	4-$EtOOCC_6H_4$	4-$OMeC_6H_4$	2	93
11	4-$EtOOCC_6H_4$	2-MeC_6H_4	2	99
12	2-NCC_6H_4	4-MeC_6H_4	10	71
13[b]	2-$MeOC_6H_4$	4-$F_3CC_6H_4$	6	87
14	2-Naph	Ph	2	94
15[c]	2-Naph	4-$MeOC_6H_4$	3	99
16[c]	1-Naph	4-$MeOC_6H_4$	3	94
17[d]	1,4-C_6H_4	4-FC_6H_4	6	93
18[d]	4,4′-$(C_6H_4)_2SO_2$	Ph	6	95
19[e]	4-$O_2NC_6H_4$	Ph	2	59
20[e]	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	2	75
21[e]	4-$EtOOCC_6H_4$	4-$MeOC_6H_4$	2	70

[a] General conditions: rt, aryl-OSO_2F(1.0 mmol), arylboronic acid (1.5 mmol), $Pd(OAc)_2$ (1 mol %), Et_3N (3.0 mmol), H_2O (3.0 mL), under air. [b] $Pd(OAc)_2$ (5 mol %), Et_3N (5.0 mmol). [c] $Pd(OAc)_2$ (1 mol %), Et_3N (5.0 mmol). [d] $Pd(OAc)_2$ (3 mol %), Et_3N (10.0 mmol). [e] Potassium aryltrifluoroborate (1.5 mmol). [f] Isolated yields.

Table 4. Other Types of Coupling Reactions Using OSO_2F

entry	aryl-OSO_2F	coupling partner	time (h)	yield[d] (%)
1[a]	4-$O_2NC_6H_4$	methyl acrylate	24	63
2[b]	2-$OHCC_6H_4$	phenyl acetylene	4	73
3[c]	4-$EtOOCC_6H_4$		20	69

[a] 4-Nitrophenyl fluorosulfate (2.0 mmol), methyl acrylate (4.0 mmol), $Pd(OAc)_2$ (2 mol %), dppp (3 mol %), Et_3N (2.4 mmol), DMF (5 mL), in argon at 80 °C, 24 h. [b] 2-Formylphenyl fluorosulfate (2.0 mmol), phenylacetylene (2.8 mmol), $PdCl_2(PPh_3)_2$ (2 mol %), Et_3N (5.0 mmol), DMF (0.7 mL), in argon at 80 °C, 4 h. [c] Ethyl 4-[(fluorosulfonyl)oxy]benzoate (2.0 mmol), $NiCl_2(PPh_3)_2$ (10 mol %), Zn (3.4 mmol), Bu_4NI (3.0 mmol), THF (2 mL), in argon at 70 °C, 20 h. [d] Isolated yields.

Sonogashira (Table 4, entry 2), and nickel-catalyzed homocoupling reactions (Table 4, entry 3), following the literature methods.[25] All the reactions proceeded smoothly and afforded satisfactory results as shown in Table 4.

In summary, we developed a simple, efficient procedure for the Suzuki–Miyaura cross-coupling reaction in water under mild conditions using aryl fluorosulfates, which were prepared by a clean, cheap, synthetic method, as coupling partners. Furthermore, the fluorosulfates were demonstrated to be versatile alternatives to triflates and could be widely used in organic synthesis. Further applications of this useful coupling partner are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Available full experimental details, spectroscopic data, and copies of ^1H and ^{13}C NMR for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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