ACS Catalysis
Research Article
pubs.acs.org/acscatalysis

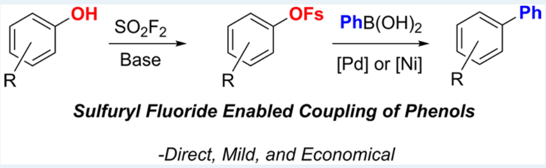
Nickel- and Palladium-Catalyzed Coupling of Aryl Fluorosulfonates with Aryl Boronic Acids Enabled by Sulfuryl Fluoride

Patrick S. Hanley,*[†] Matthias S. Ober,[†] Arkady L. Krasovskiy,[†] Gregory T. Whiteker,[‡] and William J. Kruper[†]

[†]Core R&D, The Dow Chemical Company, Midland, Michigan 48674, United States
[‡]Dow AgroSciences, LLC, Indianapolis, Indiana 46268, United States

Supporting Information

ABSTRACT: Herein are reported examples of the nickel- and palladium-catalyzed cross-coupling of aryl fluorosulfonates and aryl boronic acids. These reactions occur in good to excellent yields under mild conditions with excellent functional group compatibility employing either $Pd(OAc)_2$ and inexpensive PPh_3 or the inexpensive and readily available $NiCl_2(PCy_3)_2$. Importantly, the in situ conversion of phenol derivatives to the corresponding aryl fluorosulfonate by reaction with sulfuryl fluoride and a base and subsequent cross-coupling to form biaryls in a single pot are described. The combination of inexpensive sulfuryl fluoride and efficient catalysts reported in these methodologies will enable economical Suzuki coupling of phenols in pharmaceutical and agrochemical processes.



Sulfuryl Fluoride Enabled Coupling of Phenols

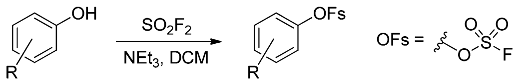
-Direct, Mild, and Economical

KEYWORDS: *sulfuryl fluoride, cross-coupling, fluorosulfonate, nickel catalysis, phenol*

Transition metal-catalyzed cross-coupling methodologies to form new carbon−carbon or carbon−heteroatom bonds have revolutionized modern organic synthesis.[1] The Suzuki−Miyaura coupling of an aryl boronic acid or ester with an aryl halide to form a new $C(sp^2)-C(sp^2)$ bond is a reliable, economical reaction that has been incorporated into processes for the preparation of specialty, agricultural, and pharmaceutical chemicals.[2] Aryl electrophiles derived from phenols offer an alternative to aryl halides in cross-coupling reactions.[3,4] Couplings of aryl triflates have been described for over two decades;[5] however, the high cost of triflic anhydride has limited the practice of this chemistry to only the most high-value materials. Recent advances with Pd[6] and Ni[7] catalysts have allowed for the coupling of aryl mesylates and tosylates with boronic acid derivatives. Nickel-catalyzed Suzuki couplings of aryl pivalates, carbamates, and sulfamates[8] have also been reported, but these systems typically require expensive, complex ligands or harsh conditions that continue to limit the utility of these methods.

Aryl fluorosulfonates were first described more than four decades ago, but the chemistry of these compounds is relatively unexplored.[9] Recently, renewed interest in the preparation of aryl fluorosulfonates from the reaction of a phenol with sulfuryl fluoride in the presence of a base was described by Sharpless and co-workers (Scheme 1).[10] Sulfuryl fluoride (SO_2F_2, bp = −55.4 °C) is produced by Dow AgroSciences, LLC and is most commonly employed as a commodity insecticide for the control of drywood termites by whole-structure fumigation.[11] Examples of palladium-catalyzed functionalization reactions of aryl and vinyl fluorosulfonates are scarce,[12] and the relative propensity of fluorosulfonates to undergo oxidative addition to palladium, compared with more well-studied aryl sulfonates and aryl halides, has not been reported.

Scheme 1. Preparation of Aryl Fluorosulfonates from Phenols and Sulfuryl Fluoride



Herein, we report the first detailed examination of the cross-coupling of aryl fluorosulfonates with aryl boronic acids catalyzed by the combination of either a palladium or nickel complex and phosphine ligand.[13] The reaction is promoted by a broad set of catalyst combinations with a variety of solvents and bases that were initially identified from a screening and response surface design of experiments (DoE). The economical catalyst combination of $Pd(OAc)_2$ and PPh_3 provides excellent conversion of aryl fluorosulfonates to biaryl products under mild conditions (60 °C) with broad functional group compatibility. In addition, we report the first nickel-catalyzed Suzuki coupling of aryl fluorosulfonates using $NiCl_2(PCy_3)_2$ in combination with $PCy_3{\cdot}HBF_4$. Finally, we show that in situ formation of aryl fluorosulfonates from phenols and SO_2F_2 followed by efficient Suzuki coupling in the same pot is possible.

To identify conditions for the coupling of aryl fluorosulfonates with aryl boronic acids, we examined the reaction of *p*-tolylfluorosulfonate (**2a**) and phenylboronic acid in the

Received: May 15, 2015
Revised: July 10, 2015
Published: July 14, 2015

DOI: 10.1021/acscatal.5b01021
ACS Catal. 2015, 5, 5041−5046

presence of a series of palladium precatalysts and phosphine ligands. To explore a broad reaction landscape in an efficient manner, we created an I-optimal DoE to examine simultaneously the effect of solvent, precatalyst, ligand, base, and the addition of water on the yield of cross-coupled product. The design included 26 unique experiments with 4 duplicates. Two precatalysts {$Pd(OAc)_2$ and CpPd(cinnamyl)} were studied along with six different ligands {PPh_3, dppf (1,3-bis(diphenylphosphino)ferrocene), dppp (1-3-bis(diphenylphosphino)propane), P(*t*-Bu)$_3$, XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), and CMPhos (2-[2-(dicyclohexylphosphino)phenyl]-1-methyl-1*H*-indole)}. In addition, two different bases (K_3PO_4 and NEt_3) and three different solvents (*t*-butanol, 1,4-dioxane and toluene) were included in the experimental design. Moreover, the effect of water as cosolvent was studied. The reactions were conducted under nitrogen in 20 mL scintillation vials with 2 mol % palladium precatalyst and 5 mol % ligand. The 30 parallel reaction mixtures were heated to 80 °C for 17 h on a heater/stirrer plate and then analyzed by gas chromatography to determine the yield of 4-phenyltoluene.

The DoE revealed that numerous palladium and ligand combinations catalyzed the Suzuki reaction of *p*-tolylfluorosulfonate. For example, 12 of the 30 reactions produced 4-phenyltoluene in >50% yield. The yield data were fitted to an empirical predictive model using JMP Pro 10.0.2 software, and the results are illustrated in Figure 1.[14] The highest yields of cross-coupled products were obtained from reactions containing CMPhos, XPhos, or PPh_3 ligands. Generally, the yields of 4-phenyltoluene that were obtained from reactions conducted with $Pd(OAc)_2$ were higher than yields obtained from reactions conducted with CpPd(cinnamyl). The choice of solvent and base did not greatly impact the outcome of the reaction. Although the model predicted the optimal coupling conditions to include $Pd(OAc)_2$ and CMPhos in the presence of water and dioxane, reactions conducted with $Pd(OAc)_2$ and PPh_3 also resulted in excellent yields of 4-phenyltoluene. Because of the low cost of PPh_3, this ligand was chosen for further optimization.

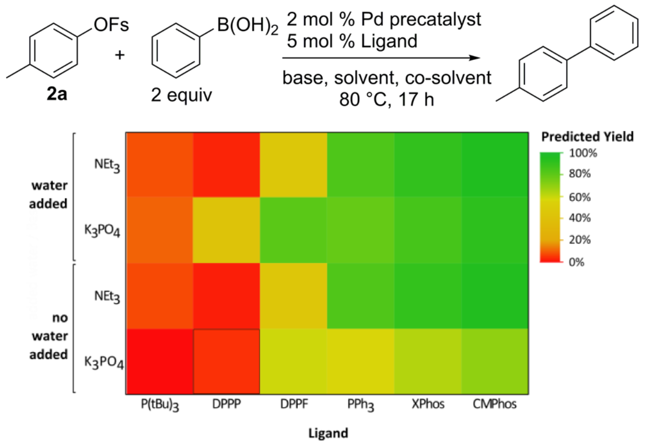
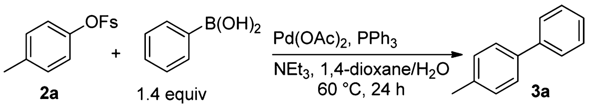


Figure 1. DoE-derived yield model.[15]

To understand the effect of the precatalyst-to-ligand ratio and boronic acid concentration on the outcome of the coupling reaction, a response surface DoE was created. The coupling of **2a** and phenylboronic acid in the presence of 1 mol % $Pd(OAc)_2$ and triethylamine in 1,4-dioxane/water was conducted at 60 °C. The amount of phenylboronic acid (1–2 equiv) and PPh_3 (1.3–2.7 mol %) added to the reaction was varied. The outcomes of these experiments revealed the optimal reaction parameters of 1.4 equiv of phenylboronic acid and 1:2.5 ratio of Pd/PPh_3.[16] Reactions conducted with less than a 1:2.5 ratio of Pd/PPh_3 resulted in formation of palladium black and decreased yields of biaryl product. Table 1 describes couplings conducted with the optimized ligand to catalyst ratio at lower catalyst loadings.

Table 1. Effect of Pd Loading on Coupling of Phenylboronic Acid and *p*-Tolyl Fluorosulfonate[a]



entry	$Pd(OAc)_2$ loading (mol %)	PPh_3 loading (mol %)	yield[b] (%)
1	1.0	2.5	100
2	0.5	1.25	100
3	0.1	0.25	59
4	0.01	0.025	17

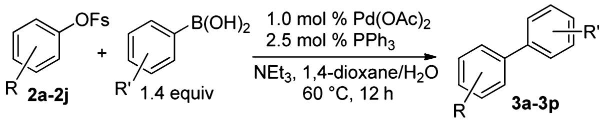
[a] General conditions: aryl fluorosulfonate (0.50 mmol); phenyl boronic acid (1.4 equiv, 0.70 mmol); NEt_3 (1.0 mmol); 1,4-dioxane (1.5 mL); water (0.3 mL). [b] Yields determined by gas chromatography using an internal standard.

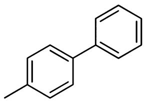
With these optimized conditions, we next evaluated the Suzuki coupling of a diverse set of aryl fluorosulfonates that spanned a range of electronic and steric properties. Generally, good to excellent isolated yields of cross-coupled products were obtained. Ether (**3b**, **3g**), ester (**3d**), amide (**3j**), and chloro (**3f**) functional groups were tolerated (Table 2). Reactions of aryl fluorosulfonates containing electron-withdrawing substituents occurred in higher yields than reactions of aryl fluorosulfonates containing electron-donating substituents. For example, the coupling of $PhB(OH)_2$ with **2c** (R = *p*-CF_3) occurred in 93% yield, whereas the analogous coupling of **2b** (R = *p*-OMe) occurred in only 33% yield. Sterically encumbered aryl fluorosulfonates **2i** and **2h** also reacted to form high yields of cross-coupled product under mild conditions. Primary amines were not tolerated by the reported reaction conditions. Finally, the coupling of the heteroaromatic 3-pyridyl fluorosulfonate **2e** occurred in 75% yield.

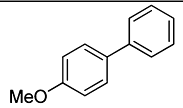
Suzuki couplings of a variety of aryl boronic acid derivatives with *p*-tolylfluorosulfonate were also demonstrated. Aryl boronic acids containing electron-donating groups (*p*-OMe) and electron-withdrawing groups (*p*-F and 3-NO_2) were tolerated. The corresponding cross-coupling reactions occurred in 67% (**3m**), 96% (**3l**), and 57% (**3o**) yield. In addition, the coupling of 4-pyridyl boronic acid with *p*-tolylfluorosulfonate occurred in 53% yield.

To understand the relative reactivity of aryl fluorosulfonates and other common aryl electrophiles, a series of competition experiments was conducted. A 1:1:1 mixture of aryl fluorosulfonate, phenyl boronic acid, and an alternative aryl electrophile was reacted with $Pd(OAc)_2$, PPh_3, and K_3PO_4. The conversion of each electrophile and the yield of 4-phenyltoluene are shown in Table 3. The relative reactivity of electrophiles examined in this coupling reaction follows the trend I > Br > OTf ≅ OFs ≫ Cl, OTs, OMs. The reactivity of the fluorosulfonate is most analogous to that of the triflate.

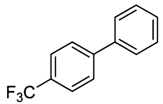
Table 2. Palladium-Catalyzed Coupling of Aryl Fluorosulfonates and Aryl Boronic Acids[a,b]



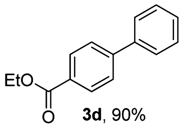

3a, 92%



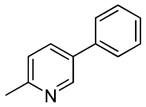
3b, 33%



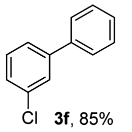
3c, 93%



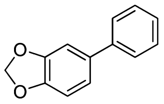
3d, 90%

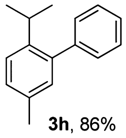


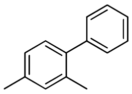
3e, 75%

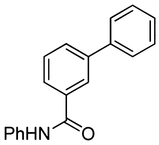


3f, 85%

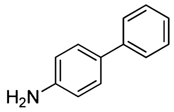

3g, 93%


3h, 86%

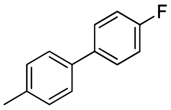

3i, 77%



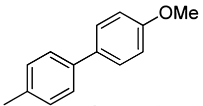
3j, 64%



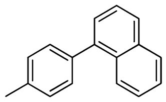
3k, 0%

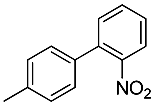


3l, 96%

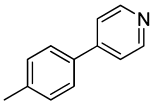


3m, 67%


3n, 97%



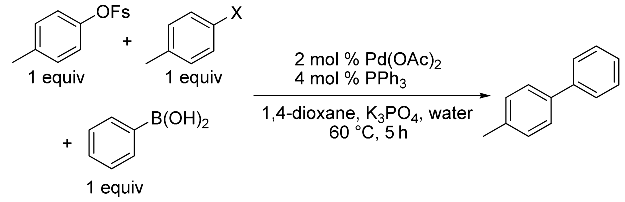
3o, 57%



3p, 53%

[a] General conditions: aryl fluorosulfonate (2.5 mmol); phenyl boronic acid (1.4 equiv, 3.5 mmol); $Pd(OAc)_2$ (1 mol %); PPh_3 (2.5 mol %); NEt_3 (2 equiv, 5.0 mmol); 1,4-dioxane (7.5 mL); water (1.5 mL). [b] Isolated yields.

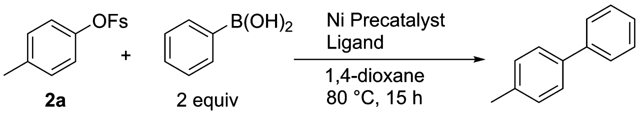
Table 3. Competitive Suzuki Reactions between Aryl Fluorosulfonates and Common Aryl Electrophiles



entry	X	conversion Ar−OFs (%)	conversion Ar−X (%)	yield (%)[a]
1	OFs	94		85
2	I	8	97	76[b]
3	Br	25	82	84[b]
4	Cl	84	8	78
5	OTf	48	56	86
6	OTs	91	1	85
7	OMs	92	3	86

[a] Yields determined by gas chromatography. [b] Approximately 10% homocoupled product 4,4′-dimethyl-1,1′-biphenyl observed.

Table 4. Nickel-Catalyzed Coupling of Aryl Fluorosulfonates and Phenyl Boronic Acid[a]



entry	Ni source (mol %)	ligand (mol %)	base	yield[b] (%)
1	$NiCl_2(PCy_3)_2$ (5)	PCy_3 (10)	K_3PO_4	59
2	$NiCl_2(PCy_3)_2$ (5)		K_3PO_4	57
3	$NiCl_2(PPh_3)_2$ (5)	PPh_3 (10)	K_3PO_4	5
4	$NiCl_2$(dppe) (5)	dppe (5)	K_3PO_4	54
5	$Ni(COD)_2$ (5)	PCy_3 (10)	K_3PO_4	22
6	$Ni(COD)_2$ (5)	PPh_3 (10)	K_3PO_4	7
7	$Ni(COD)_2$ (5)	SIPr·HCl (10)	K_3PO_4	16
8	$Ni(COD)_2$ (5)	$PCy_3\cdot HBF_4$ (10)	K_3PO_4	66
9	$NiCl_2(PCy_3)_2$ (5)		Na_2CO_3	60
10	$NiCl_2(PCy_3)_2$ (5)		NEt_3	0
11	$NiCl_2(PCy_3)_2$ (5)		NaO*t*Bu	27
12	$NiCl_2(PCy_3)_2$ (3)	$PCy_3\cdot HBF_4$ (6)	K_3PO_4	91
13	$Ni(COD)_2$ (3)	$PCy_3\cdot HBF_4$ (6)	K_3PO_4	99
15	$NiCl_2(PCy_3)_2$ (1)	$PCy_3\cdot HBF_4$ (2)	K_3PO_4	96
16	$Ni(COD)_2$ (1)	$PCy_3\cdot HBF_4$ (2)	K_3PO_4	100

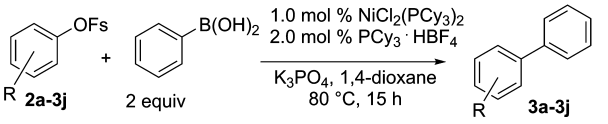
[a] General conditions: aryl fluorosulfonate (0.3 mmol); phenyl boronic acid (2.0 equiv, 0.6 mmol); Ni source; ligand; base (3 equiv, 1.5 mmol); 1,4-dioxane (2 mL). [b] Yields determined by GC using internal standard.

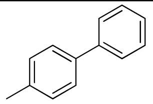
To explore further the coupling of aryl fluorosulfonates with inexpensive first-row metals, we next examined the coupling of *p*-tolylfluorosulfonate with phenylboronic acid by a series of nickel catalysts. To our knowledge, only one unsuccessful nickel-catalyzed Suzuki coupling of a vinyl fluorosulfonate has been described in the literature.[12e] We evaluated Ni(0) and Ni(II) sources in combination with phosphine ligands PCy_3 (tricyclohexylphosphine), PPh_3, and dppe (1,2-bis(diphenylphosphinoethane)), and the *N*-heteocyclic carbene ligand SiPr·HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride). The reactions were conducted in 1,4-dioxane at 80 °C in the presence of K_3PO_4, NEt_3, Na_2CO_3,or NaO*t*Bu.

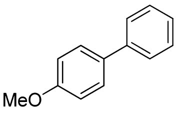
We were pleased to find that many of the nickel-catalyzed Suzuki couplings formed biaryl product (Table 4). Reactions conducted with PCy_3 in combination with $Ni(COD)_2$ or the preformed Ni(II) complex $NiCl_2(PCy_3)_2$ generated excellent yields of 4-phenyltoluene. Reactions conducted with inorganic bases K_3PO_4 and Na_2CO_3 generated higher yields than those conducted with NEt_3 or NaO*t*Bu. Interestingly, higher yields of cross-coupled product were observed from reactions conducted with lower loadings of nickel. We propose this may be the result of off-cycle nickel-mediated degradation pathways that lead to reduction of the aryl fluorosulfonate. For example, the reaction of *p*-tolylfluorosulfonate with phenylboronic acid in the presence of 1.0 mol % $NiCl_2(PCy_3)_2$ occurred in 96% yield, whereas the same reaction conducted in the presence of 5.0 mol % $NiCl_2(PCy_3)_2$ occurred in 59% yield (entries 15 and 1). Couplings catalyzed by the preformed $NiCl_2(PCy_3)_2$ complex occurred in greater yield when additional ligand was added to the reaction in the form of $PCy_3\cdot HBF_4$. Further studies were conducted with $NiCl_2(PCy_3)_2$ as a source because of its superior stability to air and moisture.

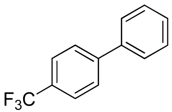
To examine the generality of this nickel-catalyzed Suzuki coupling reaction, we evaluated the Suzuki coupling of a diverse set of aryl fluorosulfonates (Table 5). Generally, good to

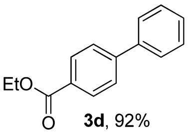
Table 5. Nickel-Catalyzed Coupling of Aryl Fluorosulfonates and Aryl Boronic Acid[a,b]

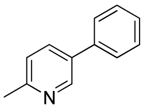


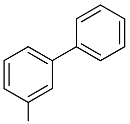

3a, 88%
83%[c]

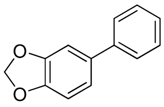

3b, 84%

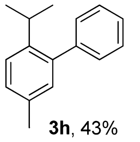

3c, 40%

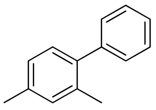

3d, 92%

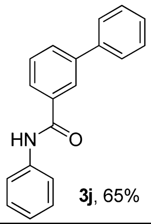

3e, 24%

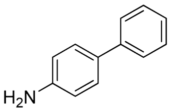

3f, 0%


3g, 90%


3h, 43%


3i, 91%


3j, 65%


3k, 53%
76%[d]

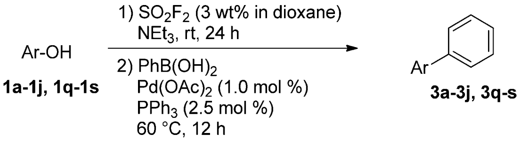
[a]General conditions: aryl fluorosulfonate (0.5 mmol); phenyl boronic acid (2.0 equiv, 1.0 mmol); $NiCl_2(PCy_3)_2$ (1 mol %); $PCy_3{\cdot}HBF_4$ (2 mol %); K_3PO_4 (3 equiv, 1.5 mmol); 1,4-dioxane (2 mL). [b]Isolated yields. [c]$NiCl_2(PCy_3)_2$ (0.5 mol %); $PCy_3{\cdot}HBF_4$ (1 mol %). [d]2.0 mol % PCy_3 added in place of $PCy_3{\cdot}HBF_4$.

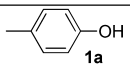
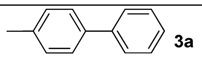
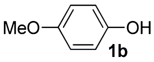
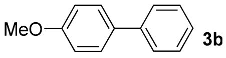
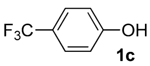
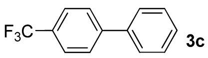
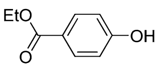
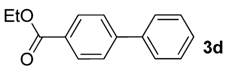
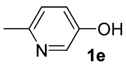
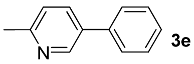
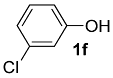
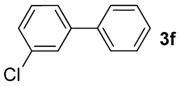
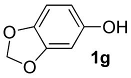
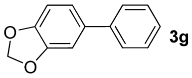
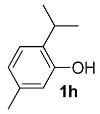
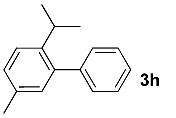
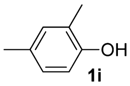
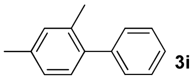
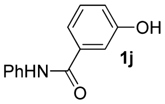
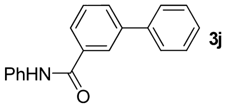
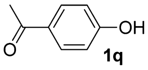
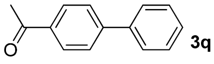
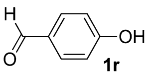
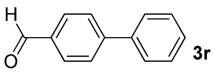
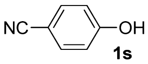
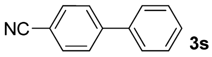
excellent yields were obtained for the nickel-catalyzed coupling, including substrates containing ether (**3b, 3g**), ester (**3d**), amide (**3j**), and primary amino (**3k**) functional groups. In contrast to reactions conducted with palladium catalysts, higher yields of cross-coupled products were obtained for electron-rich aryl fluorosulfonates than for electron-poor aryl fluorosulfonates in reactions catalyzed by $NiCl_2(PCy_3)_2$. For example, the coupling of **2b** (R = *p*-OMe) occurred in 84% yield, but the coupling of **2c** (R = *p*-CF_3) occurred in only 40% yield. The nickel system was less tolerant to sterically encumbered fluorosulfonates than the palladium system, as observed for the thymol derivative **3h** (Pd = 86%, Ni = 43% yield). Finally, in comparison with the complete lack of activity of the $Pd(OAc)_2/PPh_3$ catalyst system with the primary amine containing fluorosulfonate, $NiCl_2(PCy_3)_2$ gave **3k** in 76% yield.

Because the conversion of a phenol to an aryl fluorosulfonate with SO_2F_2 occurs in almost quantitative yield, we envisioned the conversion of phenols to biaryls in a single pot. Recently, the first examples of the direct conversion of phenols to biaryls by transition metal catalysis have been described, but they require expensive catalysts or harsh conditions.[17] To make this transformation well-suited to preparative scale reactions, we utilized solutions of SO_2F_2. Despite the low boiling point of SO_2F_2, it is moderately soluble at room temperature in organic solvents. We prepared a saturated ~3 wt % solution of SO_2F_2 in 1,4-dioxane that could be stored under ambient conditions. Addition of ~1.5 equiv of SO_2F_2 in 1,4-dioxane to *p*-cresol (**1a**) in the presence of 2 equiv of NEt_3 resulted in the quantitative conversion to **2a** after 24 h at room temperature. Any remaining SO_2F_2 was easily removed from the reaction mixture by simply sparging with N_2 gas.

Results for the one-pot conversion of phenols to the corresponding biaryl by this in situ activation with SO_2F_2 and subsequent Suzuki coupling with phenylboronic acid by a palladium catalyst are shown in Table 6. The reactions were

Table 6. One-Pot Suzuki Coupling of Phenols Enabled by Sulfuryl Fluoride[a]



Entry	Phenol	Product	Yield[b] (%)
1a 1b[c]	 **1a**	 **3a**	87 90
2	 **1b**	 **3b**	48
3	 **1c**	 **3c**	76
4		 **3d**	81
5	 **1e**	 **3e**	87
6	 **1f**	 **3f**	88
7	 **1g**	 **3g**	73
8	 **1h**	 **3h**	53
9	 **1i**	 **3i**	62
10	 **1j**	 **3j**	83
11	 **1q**	 **3q**	76
12	 **1r**	 **3r**	68
13	 **1s**	 **3s**	90

[a]General conditions: (1) phenol derivative (2.5 mmol); NEt_3 (1.2 mL; 3.4 equiv); SO_2F_2 3 wt % in 1,4-dioxane (13 mL; 1.5 equiv); (2) phenylboronic acid (1.4 equiv, 3.5 mmol); $Pd(OAc)_2$ (1 mol %); PPh_3 (2.5 mol %); NEt_3 (0.35 mL, 1 equiv); water (1.5 mL). [b]Isolated yields. [c]K_2CO_3 (8.75 mmol, 3.5 equiv) added in the place of NEt_3.

conducted in a fume hood by addition of SO_2F_2 in 1,4-dioxane to a phenol derivative and NEt_3. After stirring at ambient temperature for 24 h, the reaction mixture was sparged with N_2. Phenylboronic acid, water, PPh_3, $Pd(OAc)_2$, and additional NEt_3 were then added,[18] and the mixture was heated (60 °C) for 12 h to provide cross-coupled products in high yields. For example, the conversion of phenol to 4-phenyltoluene occurred in 87% isolated yield. K_2CO_3 can be used in place of NEt_3 for the entire single pot sequence (entry 1b—90% yield).

The single pot palladium-catalyzed Suzuki coupling of phenols demonstrated broad functional group compatibility; however, the steric and electronic properties of the substituted phenols had a greater effect on the outcome of the reaction than in the corresponding couplings of isolated fluorosulfonates. The conversion of more sterically encumbered phenols to fluorosulfonates occurred more slowly in the absence of a large excess of sulfuryl fluoride. For example, the reaction of thymol (**1h**) with sulfuryl fluoride (1.5 equiv) resulted in ~70% conversion to the fluorosulfonate, affording 53% yield of biaryl product. Higher yields in these cases can be obtained by using a larger excess of SO_2F_2. Generally, the couplings of neutral or electron-deficient phenols occurred in higher yields than couplings of electron-rich phenols. Incomplete conversion of the more electron-rich fluorosulfonate intermediates in entries 2 and 9 was observed. Preliminary results indicate that analogous one-pot couplings are also possible using nickel catalysts.

Here, we have described optimized Suzuki couplings of boronic acids and aryl fluorosulfonates using Pd and Ni phosphine catalyst combinations. These reactions occur under mild conditions with inexpensive ligands and tolerate a wide range of functional groups. The relative reactivity of the aryl fluorosulfonate toward palladium-catalyzed coupling with a boronic acid was shown to be most similar to that of an aryl triflate or bromide, and the reactivity of aryl fluorosulfonates was much greater than that of an aryl mesylate or tosylate. In addition, these reactions are catalyzed by the first-row metal nickel, which is more than 3 orders of magnitude less expensive than palladium. The reactivity of these two catalyst systems is complementary: palladium catalysts give higher yields with electron-poor aryl fluorosulfonates, and nickel catalysts give higher yields with electron-rich aryl fluorosulfonates. Importantly, direct conversion of a phenol to a biaryl via palladium-catalyzed Suzuki coupling was enabled by in situ fluorosulfonate formation with sulfuryl fluoride.

Although previously reported aryl sulfonates undergo oxidative addition and subsequent Suzuki coupling with rates and yields similar to those of aryl halides, the industrial implementation of these sulfonates as cross-coupling reagents has been limited by three factors: (1) the high cost and stability issues associated with triflic anhydride; (2) the requirement for specialized, expensive ligands for coupling less reactive sulfonates, such as tosylates and mesylates; and (3) the additional isolation step needed for the conversion of a phenol to the reactive coupling partner. The chemistry described in this report provides the first general methodology to directly utilize a phenol as an electrophile in Suzuki coupling reactions in a mild and economical manner. The bulk availability of sulfuryl fluoride, combined with its high hydrolytic stability, provides an attractive commercial alternative to triflic anhydride. Future work will explore fluorosulfonate electrophiles in additional transition metal-catalyzed coupling reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01021.

General experimental details, DoE data analysis, and ^1H and ^{13}C NMR spectra for the fluorosulfonates **2a**−**2j** and biaryls **3a**−**3m** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pshanley@dow.com.

Notes

The authors declare no competing financial interests.

■ ACKNOWLEDGMENTS

The authors thank Tina Staton and Tim Gallagher for assistance with CM3 robot operations (see the Supporting Information for details) and purification of organic products. We also thank John O'Brien for HRMS characterization.

■ REFERENCES

(1) (a) *New Trends in Cross Coupling*; Colacot, T. J., Ed.; Royal Society of Chemistry: Cambridge, 2015. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004. (c) *Topics in Current Chemistry*; Miyaura, N.; Ed.; Springer-Verlag: New York, 2002; Vol. *219*. (d) Hassan, J.; Sèvignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(2) (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.

(3) Rappoport, Z., Ed.; *The Chemistry of Phenols*; John Wiley& Sons Ltd: Chichester, 2003.

(4) (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Yu, D.; Li, B.; Shi, Z. *Acc. Chem. Res.* **2010**, *43*, 1486.

(5) (a) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (b) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.

(6) (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (b) So, C.; Lau, C.; Kwong, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059. (c) So, C.; Lau, C.; Chan, A. S. C.; Kwong, F. *J. Org. Chem.* **2008**, *73*, 7731. (d) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954. (e) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346. (f) Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2010**, *75*, 5109. (g) Wang, Z.; Chen, G.; Shao, L. *J. Org. Chem.* **2012**, *77*, 6608. (h) Molander, G.; Beaumard, F. *Org. Lett.* **2011**, *13*, 1242. (i) Chung, K.; So, C.; Wong, S.; Luk, C.; Zhou, Z.; Lau, C.; Kwong, F. *Chem. Commun.* **2012**, *48*, 1967.

(7) (a) Percec, V.; Bae, J.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060. (b) Kuroda, J.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, *2009*, 2251. (c) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049. (d) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447. (e) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29.

(8) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (b) Guan, B.; Wang, Y.; Li, B.; Yu, D.; Shi, Z. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (c) Li, Z.; Zhang, S.; Fu, Y.; Guo, Q.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815. (d) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (e) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750. (f) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352. (g) Xu, L.; Li, B.; Wu, Z.; Lu, X.; Guan, B.; Wang, B.; Zhao, K.; Shi, Z. *Org. Lett.* **2010**, *12*, 884. (h) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 1507. (i) Leowanawat, P.; Zhang, N.; Resmerita, A.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2011**, *76*, 9946.

(9) (a) Hedayatullah, M.; Guy, A.; Denivelle, L. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1974**, *278*, 57. (b) Firth, W. C. (American Cyanamid Company); *Aryl Sulfate Polymers and Methods for their Production*; U.S. Patent 3,733,304, May 15, 1973. (c) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, *2*, 85.

(10) (a) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430. (b) Dong, J.; Sharpless, K. B.; Kwisnek, L.; Oakdale, J. S.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 9466.

(11) All manipulations of sulfuryl fluoride should be conducted in a well-ventilated fume hood. We recommend the use of a specialty sulfuryl fluoride detector for lab scale use.

(12) (a) Roth, G. P.; Fuller, C. E. *J. Org. Chem.* **1991**, *56*, 3493. (b) Roth, G. P.; Thomas, J. A. *Tetrahedron Lett.* **1992**, *33*, 1959. (c) McGuire, M. A.; Sorenson, E.; Owings, F. W.; Resnick, T. M.; Fox, M.; Baine, N. H. *J. Org. Chem.* **1994**, *59*, 6683. (d) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550. (e) Pridgen, L.; Huang, G. K. *Tetrahedron Lett.* **1998**, *39*, 8421.

(13) During the preparation of this manuscript, Sharpless, Jiang, and coworkers reported ligand-free Pd-catalyzed coupling of aryl fluorosulfonates and aryl boronic acids: Liang, Q.; Xing, P.; Huang, Z.; Dong, Z.; Sharpless, K. B.; Li, X.; Jiang, B. *Org. Lett.* **2015**, *17*, 1942.

(14) According to our statistical model, the effect of the reaction solvent on the reaction yield is statistically insignificant within the boundaries of our DoE; hence, the variable “solvent” was excluded from the refined model. The variable “metal precursor” was borderline statistically insignificant (Prob > $|t|$ = 0.094); thus, in Figure 1, the average values of both metal precursors are shown.

(15) *JMP, Version 10.0.2*; SAS Institute Inc.: Cary, NC, 1989−2007.

(16) Optimal conditions are defined as the minimum amount of phenylboronic acid and PPh_3 required for yields > 90%.

(17) (a) Ikawa, T.; Saito, K.; Akai, S. *Synlett* **2012**, *23*, 2241. (b) Chen, L.; Lang, H.; Fang, L.; Zhu, M.; Liu, J.; Yu, J.; Wang, L. *Eur. J. Org. Chem.* **2014**, *2014*, 4953.

(18) The single-pot Suzuki couplings were conducted in 30 mL scintillation vials. Following the conversion of the phenol to the aryl fluorosulfonate, excess SO_2F_2 was removed by sparging N_2 through the reaction mixture. The vials were transferred to a N_2-filled glovebox for addition of phenylboronic acid, water, PPh_3, and $Pd(OAc)_2$ and NEt_3. The vials were then capped and removed from the glovebox for overnight heating.