

Nickel- and Palladium-Catalyzed Cross-Coupling of Aryl Fluorosulfonates and Phosphites: Synthesis of Aryl Phosphonates

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The synthesis of aryl phosphonates via nickel and palladiumcatalyzed cross-coupling of aryl fluorosulfonates and phosphites is described. The products were obtained in good to excellent yields under mild conditions with broad functional group compatibility, employing either Pd(OAc)₂ and DPEPhos or the readily available NiCl₂(dme) and Xantphos as catalytic systems. Noteworthily, the present C(sp²)–P bond formation method could be applied to the direct conversion of phenols to the corresponding aryl phosphonates in one pot via reaction of phenols with SO₂F₂ and subsequent palladium-catalyzed crosscoupling.

Arvl phosphonates are among the most valuable compounds in organic synthesis^[1] due to their widespread use in numerous practical applications such as pesticide synthesis, material preparations, and as ligands and catalysts, ^[2,3] which has aroused a growing interest in their synthesis in the past decades.^[4] In particular, the pioneering work by Hirao in 1981 prompted great research interest in expanding the scope of the C-P bond-forming process for the synthesis of aryl phosphonates.^[5,6] Among the numerous synthetic procedures, the metal-catalyzed cross-coupling of various aryl halides,^[7] aryl sulfonates,^[8] silanes,^[9] diazonium salts,^[10] pivalates^[11] and organobismuth compounds^[12] with secondary phosphines and phosphine oxides have been widely used. These methods have greatly extended the scope of organic coupling partners to participate in the formation of C-P bonds. However, the toxicity, cost, and limited efficiency of these approaches hinder their practical application in organic chemistry. [13,14]

Meanwhile, the cross-coupling of aryl fluorosulfonates has recently emerged as a powerful tool for the construction of organic molecules. As alternatives to halides or triflates, aryl fluorosulfonates have great potential in transition metal-catalyzed cross-coupling reactions due to their low cost, low toxicity, and reliable preparation from phenol and sulfurylfluoride (SO_2F_2) , which is abundant and inexpensive.^[15–17] As has been amply demonstrated, the aryl fluorosulfonate bond can

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Hangzhou 310012, P. R. China Supporting information for this article is available on the WWW under be successfully deployed to accomplish direct metal insertion into the typically inert C-O moiety. Furthermore, aryl fluorosulfonates have proved effective as precursors to form C-C, C-N, C-H, and C-F bonds with high predictability via metal-catalyzed C–O cleavage.^[18,20] Such bond forming reactions involving readily accessible aryl fluorosulfonates significantly expand the portfolio of electrophiles available for cross-coupling under synthetically attractive redox-neutral conditions.^[21] As the electrophilic partner, any fluorosulfonates have been used in Negishi and Still cross-couplings^[22] and palladium-catalyzed alkoxy carbonylation reactions (Scheme 1a).^[23] Researchers in the group of Jiang and Hanley have independently reported metal-catalyzed cross-couplings such as Suzuki and Buchwald -Hartwig amination couplings using arvl fluorosulfonates (Scheme 1b).^[24-26] Therefore, we envisioned that aryl fluorosulfonates could be utilized in the formation of $C(sp^2)$ -P bonds.

Herein, we disclose the first palladium and nickel-catalyzed cross-coupling of aryl fluorosulfonates with phosphites to obtain aryl phosphonates in good to excellent yields. Using a combination of Pd(OAc)₂ and DPEPhos as a catalyst, the cross-coupling provided excellent conversion of aryl fluorosulfonates to aryl phosphonate products under mild conditions with broad functional group compatibility. In addition, the first economical nickel-catalyzed C(sp²)–P bond formation of aryl fluorosulfonates using NiCl₂(dme) in combination with Xantphos is described, in which a variety of functionalized aryl fluorosulfo-

a) $\ensuremath{\text{Previous work}}\xspace$: Transition metal-catalyzed carboxylation of aryl fluorosulfonates



b) Previous work: Transition metal-catalyzed cross-coupling of aryl fluorosulfonates with coupling partners



 $\label{eq:constraint} \begin{array}{l} \textbf{This work: Ni and Pd catalyzed cross-coupling of aryl fluorosulfonates with phosphites} \end{array}$



Scheme 1. Transition metal-catalyzed cross-coupling reaction

https://doi.org/10.1002/ejoc.202001485

Chemistry Europe European Chemical Societies Publishing

nates and diverse phosphites were tolerated. Finally, we developed a straightforward *P*-arylation of phenol by in situ formation of the corresponding aryl fluorosulfonate followed by efficient $C(sp^2)$ —P bond coupling for the synthesis of aryl phosphonates in one pot. Overall, the present method is an efficient and powerful approach for the synthesis of aryl phosphonates from naturally abundant phenol.

To test the feasibility of this C(sp²)-P cross-coupling method, we conducted a preliminary study using *p*-biphenyl fluorosulfonate 1a and dibutyl phosphite 2a as model substrates. Initially, a series of phosphine ligands were explored (Table 1). To our delight, using Pd(OAc)₂/PPh₃ as a catalyst and Cs₂CO₃ as a base in THF at 80 °C for 12 h led to the desired product 3a in 20% yield (Table 1, entry 1). Encouraged by this result, we further examined the effect of ligand, base, solvent, and temperature on the reaction. We found that the type of ligand was vital for this reaction. Thus, the product yield was increased to 42% when using BINAP as a ligand (Table 1, entry 2). Gratifyingly, DPEPhos proved to be the best ligand, affording the desired product in 89% yield (Table 1, entries 4). Then, using DPEPhos as the ligand of choice, a series of bases were examined. Among the various bases screened, K₂CO₃ afforded the best result, producing 3a in 96% yield (Table 1, entry 6). Meanwhile, a slight decrease in the vield of 3a was observed using Na₂CO₃ as a base (Table 1, entry 5), and the use of K₃PO₄ resulted in a lower yield of 67% (Table 1, entry 7). In contrast, only a trace amount of the product was detected when CsF was used as a base under the same conditions (Table 1, entry 8). Other organic bases such as Et₃N and DBU gave the target product in 90% and 88% yield, respectively (Table 1, entries 9 and 10). Replacing THF as a solvent with DMF, toluene, DMSO, or 1, 4-dioxane decreased the yield (Table 1, entries 11-14). The reaction temperature also affected this cross-coupling. Thus, the yield of 3a decreased slightly

coupling reaction.[a] o″Bu [Pd]/L, Base OⁿBu Solvent (0.1 M), T Ph Ph 1a 2a 3a Yield [%]^[b] Entry Base Solvent L 1 PPh₃ Cs₂CO₃ THF 20 2 BINAP Cs₂CO₃ THF 42 Cs₂CO₃ 3 72 **Xantphos** THF 4 89 DPEPhos Cs₂CO₃ THF 5 DPFPhos Na₂CO₂ 74 THF 6 **DPEPhos** K₂CO₃ THF 96 7 DPEPhos K₃PO₄ THF 67 8 **DPEPhos** CsF THF Trace 9 **DPEPhos** Et₃N THF 90 10 88 THF DPEPhos DBU 11 **DPEPhos** K₂CO₃ DMF 77 12 DPEPhos K₂CO₂ Toluene 55 13 DPEPhos K₂CO₃ DMSO 92 14 DPFPhos K₂CO₃ 1,4-dioxane 86 [a] Reaction conditions: 1 a (0.2 mmol), 2 a (0.3 mmol, 1.5 equiv.), Pd(OAc),

Table 1. Optimization of conditions for the palladium-catalyzed cross-

[a] Reaction conditions: Ta (0.2 mmol), 2a (0.3 mmol, 1.5 equiv.), $Pd(OAC)_2$ (5 mol%), ligand (6 mol%), base (0.4 mmol, 2.0 equiv.) and solvent (2.0 mL) at 80 °C for 12 h. [b] Isolated yield.

when the temperature was raised or lowered, and no reaction occurred at room temperature.^[27] Finally, the optimal conditions for this $C(sp^2)$ —P bond cross-coupling reaction for the synthesis of aryl phosphonates were set as follows: 5 mol% Pd(OAc)₂, 6 mol% DPEPhos, and 2.0 equiv. of K₂CO₃ as a base at 80 °C in THF.

Next, considering the economic advantages of using nickel as a catalyst, we investigated its ability to promote the C(sp²)-P bond construction via the cleavage of the C–O bond of aryl fluorosulfonates. Thus, we examined the cross-coupling of pbiphenyl fluorosulfonate 1 a with dibutyl phosphite 2 a using a series of nickel catalysts (Table 2), in particular, stable Ni(II) sources such as NiCl₂(PPh₃)₂, NiCl₂(PCy₃)₂, NiCl₂(dppe) and NiCl₂(dme) in combination with various phosphine ligands including PPh₃, BINAP, dppe, dppf, DPEPhos, PCy₃·HBF₄, and Xantphos. After extensive attempts, we were pleased to find that the use of NiCl₂(dme) (5 mol%), Xantphos (6 mol%), Et₃N (2.0 eq.) and Zn (2.0 eq.) in DMF (2.0 mL) at 100 $^\circ$ C for 12 h provided the target product 3a in an excellent yield of 98% (Table 2, entry 1). Unfortunately, using NiCl₂(PPh₃)₂ instead of NiCl₂(dme) entirely suppressed the process (Table 2, entry 2), and NiCl₂(dppe) generated a moderate yield of the desired product (Table 2, entry 3). The reaction conducted with NiCl₂(PCy₃)₂ as a catalyst occurred in a remarkably poor yield under the same condition (Table 2, entry 4). Changing the ligand to DPEPhos or PPh₃ also decreased the yield (Table 2, entries 5 and 6). These results imply that the choice of the nickel source and the ligand played a pivotal role in the reaction. Meanwhile, replacing the solvent or the base did not improve the reaction efficiency (Table 2, entries 7 and 8). The reaction also proceeded smoothly at lower and higher temperatures, although the yield decreased slightly (Table 2, entries 9 and 10). Finally, a control experiment indicated that the reducing agent was essential for this cross-coupling since the target product was not obtained in the absence of Zn (Table 2, entry 11).[27]

Table 2. Optimization of conditions for the nickel-catalyzed cross-coupling reaction. $\ensuremath{^{[a]}}$		
Ph 1a	DFs O NiCl ₂ (dme) (5 mol%) ⁺ H [·] P ⁻ O ⁿ Bu Xantphos (6 mol%), Zn (⁻ Et ₃ N (2.0 eq.), DMF (0.1 2a 100 °C, 12 h	1.5 eq.) M) Ph O'Bu ^P 3a
Entry	Variation from standard conditions	Yield [%] ^[b]
1	none	98
2	NiCl ₂ (PPh ₃) ₂ instead of NiCl ₂ (dm	e) 52
3	NiCl ₂ (dppe) instead of NiCl ₂ (dm	e) 0
4	NiCl ₂ (PCy) ₂ instead of NiCl ₂ (dme	e) 4
5	DPEPhos instead of Xantphos	74
6	PPh ₃ instead of Xantphos	9
7	K ₂ CO ₃ instead of Et ₃ N	19
8	THF instead of DMF	81
9	Decreacing the temp. to 80 °C	85
10	Increasing the temp. to 120 $^\circ$ C	90
11	Without Zn	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv.), NiCl₂ (dme) (5 mol%), Xantphos (6 mol%), Et₃N (0.4 mmol, 2.0 equiv.), Zn (0.3 mmol, 1.5 equiv.) and DMF (2.0 mL) at 100 $^{\circ}$ C for 12 h. [b] Isolated yield.

With these optimized reaction conditions in hand, the substrate scope of aryl fluorosulfonates for the construction of C(sp²)–P bonds was investigated. Gratifyingly, the scope of the reaction was very broad and accommodated a variety of functions in the aryl fluorosulfonates and the phosphites. As summarized in Scheme 2, the reaction conditions were compatible with electronically and sterically diverse aryl fluorosulfonates, bearing a wide range of functional groups and synthetic handles including biaryls, ethers, esters, nitriles, ketones, aryl, halides, naphthalenes, and heterocycles. It is worth mentioning that any fluorosulfonates containing electron-withdrawing functional groups were converted to the corresponding aryl phosphonates in higher yields than aryl fluorosulfonates containing electron-donating groups under these reaction conditions. Generally, palladium and nickel catalysis afforded comparable yields in the majority of the examples examined. However, the transformation of 4-CN aryl fluorosulfonates was



 $\begin{array}{l} \label{eq:scheme 2. Substrate scope. Reaction conditions: [Pd]: 1 (0.2 mmol), 2 \\ (0.3 mmol, 1.5 equiv.), Pd(OAc)_2 (5 mol%), DPEPhos (6 mol%), K_2CO_3 \\ (0.4 mmol, 2.0 equiv.) in THF (2.0 mL) at 80 °C for 12 h; [Ni]: 1 (0.2 mmol), 2 \\ (0.3 mmol, 1.5 equiv.), NiCl_2(dme) (5 mol%), Xantphos (6 mol%), Et_3N \\ (0.4 mmol, 2.0 equiv.), Zn (0.3 mmol, 1.5 equiv.) and DMF (2.0 mL) at 100 °C \\ for 12 h. [b] Isolated yield. See the SI for full details. \\ \end{array}$



much more effective using the Ni-catalyst system, whereas the latter showed relatively low reactivities towards halide-substituted fluorosulfonates compared with the Pd-catalyst system. Furthermore, H-phosphites with different alkyl and alkoxy groups could also participate in the reaction with aryl fluorosulfonates smoothly, affording the corresponding cross-coupling products in excellent yields. In general, the inexpensive nickel catalyst provided a complementary scope to the Pd-catalyzed C(sp²)–P bond formation.

Finally, we envisioned that the present method could be used for the direct conversion of phenols to the corresponding aryl phosphonates in one pot. A balloon full of SO_2F_2 gas was used to quantitatively convert phenols into **1a** in the presence of THF and 1.2 equiv. of Et₃N after 6 h at room temperature. The remaining SO_2F_2 was easily removed from the system before the subsequent cross-coupling reaction by simply sparging with nitrogen. Surprisingly, using the palladium catalyst in this onepot synthesis afforded the corresponding aryl phosphonates in good yields from a variety of substituted phenol and phosphites (Scheme 3).

In summary, we report the successful $C(sp^2)$ –P crosscoupling between aryl fluorosulfonates and phosphites catalyzed by a combination of palladium and DPEPhos or nickel and Xantphos. The reaction proceeded efficiently to produce a broad range of aryl phosphonates under mild conditions.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cleavage reactions · Cross-coupling · Nickel · Palladium · Phosphorylation

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- [27] Full details of the initial reaction are available in the supporting information.

Manuscript received: November 12, 2020 Revised manuscript received: December 29, 2020

Accepted manuscript online: December 30, 2020