Palladium-Catalyzed One-Pot Cross-Coupling of Phenols Using Nonafluorobutanesulfonyl Fluoride

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Abstract: Palladium-catalyzed coupling reactions, such as the Suzuki–Miyaura, Sonogashira, Stille, and Buchwald–Hartwig couplings, of phenols using nonafluorobutanesulfonyl fluoride (NfF) are described. These reactions proceeded through the in situ nonaflation of phenols.

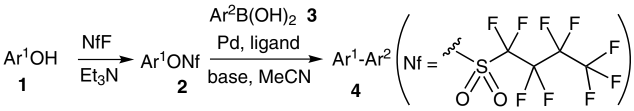
Key words: phenol, cross-coupling, palladium, boronic acid, nonaflate

Pd-catalyzed cross-couplings are extremely powerful reactions for C–C, C–N, and C–O bond formations.[1] Although only aryl iodides and bromides, except for certain activated aryl chlorides, had been applied to the coupling reactions until 20 years ago, aryl chlorides, the more useful and readily available aryl halides, are getting more and more common in coupling chemistry.[2]

On the other hand, the coupling reactions of aryl triflates[3] and nonaflates[4] are particularly attractive due to the ubiquitous presence of their starting materials – phenols – in both the natural and synthetic worlds. Moreover, the phenol derivatives may exhibit an orthogonal reactivity to the aryl halides. In recent days, the coupling reactions of significantly cheaper and more stable, but much less reactive aryl tosylates[5] and mesylates,[6] have been reported using new catalytic systems. However, the use of the aryl sulfonates limits their efficiency of the overall yield and step economy. Although several direct coupling reactions of phenols have been reported, these couplings could be applied to only limited specific substrates.[7,8] Therefore, the development of a more reliable and general direct method for the phenol coupling has been eagerly anticipated.

In this communication, we report the general, user-friendly, direct cross-coupling reactions of phenols using nonafluorobutanesulfonyl fluoride (NfF).[4,9] The coupling products were obtained by one operation of the phenols in a single flask.

Knochel et al. reported the Suzuki–Miyaura and Negishi coupling reactions of aryl nonaflates **2** prepared from phenols **1** to obtain biaryls **4** (Scheme 1).[10] This protocol should be useful because a broad range of phenols could be applied to these coupling reactions. Aryl nonaflates **2** showed a much higher reactivity than the corresponding aryl tosylates and mesylates and a slightly higher reactivity than the triflates. On the other hand, the isolation of sulfonates **2** might make this protocol less attractive. Recently, we reported a domino process for the direct preparation of benzynes from *o*-(trimethylsilyl)phenols, which was initiated by the nonaflation of phenolic hydroxyl groups using an air-stable and less expensive sulfonylating reagent – NfF.[9c] In a similar manner, we envisioned the domino nonaflation–cross-coupling reaction of phenols **1** using NfF.



Scheme 1 Stepwise Suzuki–Miyaura coupling of phenols **1**

We first optimized the reaction conditions of the domino process that combined the nonaflation of *p*-cresol **1a** using NfF and the Suzuki–Miyaura coupling of the in situ generated nonaflate **2a** with phenylboronic acid **3a** (or its pinacol ester **3a′**, Table 1). We found that **1a** was smoothly nonaflated using Cs_2CO_3 (1.5 equiv) with NfF (1.5 equiv),[9] and the produced nonaflate **2a** was partially coupled with **3a′** by Pd/SPhos[11] to give the expected **4a** (Table 1, entries 1–4). XPhos was a much less effective ligand than SPhos (Table 1, entry 2), and MeCN was the best solvent for the coupling reaction (Table 1, entries 1, 3, and 4). However, the reaction was not completed even after 91 hours using **3a′**. Interestingly, in spite of its acidic property of boronic acid **3a**, **1a** was completely nonaflated in the presence of **3a** instead of **3a′** under basic conditions (1.5 equiv of Cs_2CO_3), and the higher conversion into **4a** was obtained (Table 1, entries 1 and 5). $Pd_2(dba)_3$ was a better palladium source for the Suzuki–Miyaura coupling than $Pd(OAc)_2$ and $Pd(dba)_2$ (Table 1, entries 5–7), and the use of K_2CO_3 and K_3PO_4 gave **4a** in lower yields (Table 1, entries 9 and 10). Finally, the complete conversion to **4a** from **1a** and **3a** was achieved using Cs_2CO_3 (3.0 equiv) and $Pd_2(dba)_3$ (1 mol%) in MeCN (Table 1, entry 8). The complete conversion was also obtained using Ph_3P (Table 1, entry 11), while a similar reaction using dppf stopped around half conversion (Table 1, entry 12).

With the optimized conditions in hand, we explored the scope of the direct Suzuki–Miyaura coupling of phenols **1** with arylboronic acids **3** using SPhos (Table 2). Phenols bearing electron-neutral (**1a**), electron-donating (**1b**),[12] and electron-withdrawing groups (**1c** and **1d**) at the *para*

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Table 1 Optimization of Reaction Conditions of Suzuki–Miyaura Coupling of *p*-Cresol **1a** with Boronic Acid **3a** or Boronate **3a′**[a]

$$\underset{\mathbf{1a}}{\text{4-TolOH}} + \begin{matrix}\text{PhB(OH)}_2\ \mathbf{3a}\\ \text{or}\\ \text{PhBpin}\ \mathbf{3a'}\end{matrix} \xrightarrow[\text{base, MeCN}]{\substack{\text{NfF}\\ \text{Pd, SPhos}^{b}}} \underset{\mathbf{4a}}{\text{4-TolPh}} \left(+ \underset{\mathbf{2a}}{\text{4-TolONf}} \right)$$

Entry	3	Pd cat.	Base	Solvent	Time (h)	Ratio of **4a**/**2a**[c]
1	**3a′**	$Pd(OAc)_2$	Cs_2CO_3	MeCN	46	60:40
2[d]	**3a′**	$Pd(OAc)_2$	Cs_2CO_3	MeCN	15	2:98
3	**3a′**	$Pd(OAc)_2$	Cs_2CO_3	THF	23	37:63
4	**3a′**	$Pd(OAc)_2$	Cs_2CO_3	DMF	23	19:81
5	**3a**	$Pd(OAc)_2$	Cs_2CO_3	MeCN	14	75:25
6	**3a**	$Pd(dba)_2$	Cs_2CO_3	MeCN	18	92:8
7	**3a**	$Pd_2(dba)_3$	Cs_2CO_3	MeCN	19	96:4
8	**3a**	$Pd_2(dba)_3$	Cs_2CO_3[e]	MeCN	18	100:0
9	**3a**	$Pd_2(dba)_3$	K_2CO_3	MeCN	20	45:55
10	**3a**	$Pd_2(dba)_3$	K_3PO_4	MeCN	20	40:60
11[f]	**3a**	$Pd_2(dba)_3$	Cs_2CO_3[e]	MeCN	24	100:0
12[g]	**3a**	$Pd_2(dba)_3$	Cs_2CO_3[e]	MeCN	24	50:50

[a] Reaction conditions: **1a** (1.0 equiv), **3a** or **3a′** (1.5 equiv), NfF (1.5 equiv), base (1.5 equiv), Pd (2 mol%), SPhos[b] (2 mol%) in MeCN (0.5 M) at 60 °C; **1a** was completely consumed in all cases.

[b] SPhos = 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

[c] Determined by ^{1}H NMR spectroscopy.

[d] 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) was used instead of SPhos.

[e] Conditions: 3.0 equiv of Cs_2CO_3 were used.

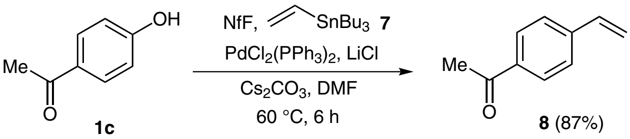
[f] Triphenylphosphine (PhP_3) was used instead of SPhos.

[g] 1,1′-Bis(diphenylphosphino)ferocene (dppf) was used instead of SPhos.

position were directly converted into biaryls **4a**–**d** in 86–92% isolated yields (Table 2, entries 1–4). In the presence of an aliphatic hydroxyl group, the phenolic hydroxyl group of **1e** was preferentially nonaflated, and **4e** was obtained in 60% yield without using any protective group (Table 2, entry 5). The reactions of phenylboronic acid **3a** and its derivative **3b** having an electron-donating group exhibited good reactivities to give **4a**, **4f**, and **4g** in excellent yields (Table 2, entries 1, 6, and 7), while an electron-withdrawing ester group of boronic acid **3d** reduced the yield of **4h** (Table 2, entry 8). The homocoupling reactions of the boronic acids **3b** and **3d** proceeded as a side reaction when using *ortho*-isopropyl phenol **1g** and/or the *ortho*-substituted boronic acids **3e** and **3f** (Table 2, entries 10–14). Therefore, we used 3.0 equiv of **3** and obtained **4j**–**n** in 70–88% yields.

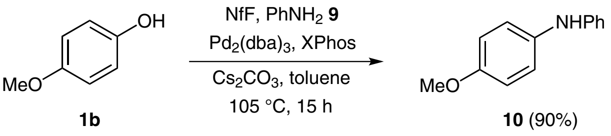
We then tried the direct Sonogashira coupling of phenols **1** with phenylacetylene (**5**, Table 3). After optimization of the reaction conditions,[13] we developed a copper-free Sonogashira coupling, because a homocoupling product of acetylene **5** was observed using CuI as an additive. The coupling reactions of phenols bearing either an electron-donating (**1b** and **1h**, Table 3, entries 1 and 4) or an electron-withdrawing group (**1c** and **1d**, Table 3, entries 2 and 3) were achieved to give the diarylacetylenes **6a**–**d** in 79–95% yields.

The direct Stille coupling of a phenol derivative **1c** with vinyl stannane **7** was attained using NfF, $PdCl_2(PPh_3)_2$, LiCl, and Cs_2CO_3 to give the corresponding styrene **8** in 87% isolated yield (Scheme 2).



Scheme 2

The direct conversion of the phenolic hydroxyl group of **1b** to an amino group was also achieved using NfF and $Pd_2(dba)_3$. It is worth noting that the hydroxyl group of **1b** was selectively nonaflated in the presence of aniline **9**, and an in situ prepared nonaflate was selectively coupled with **9** to furnish the diarylamine **10** in 90% yield (Scheme 3).



Scheme 3

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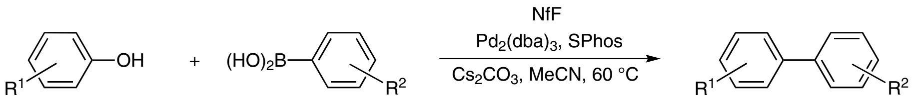
Table 2 Substrate Scope of Suzuki–Miyaura Coupling of Phenols **1** with Arylboronic Acids **3**[a]



1 **3** **4**

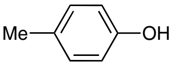
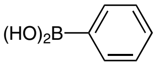
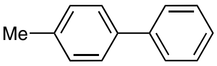
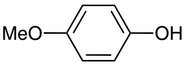
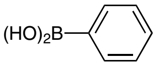
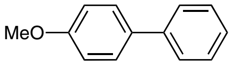
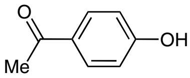
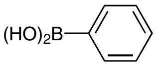
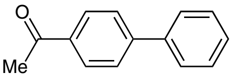
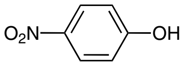
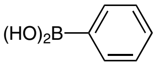
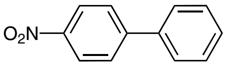
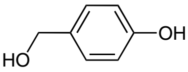
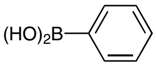
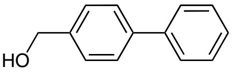
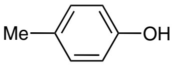
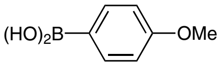
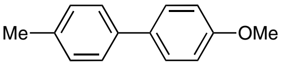
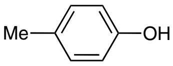
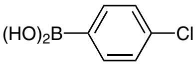
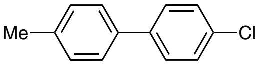
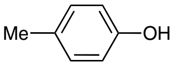
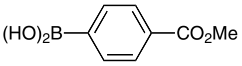
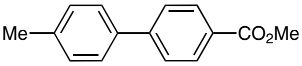
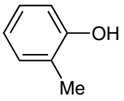
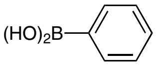
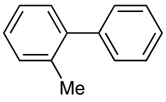
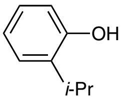
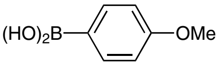
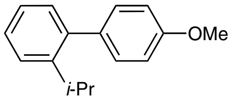
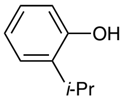
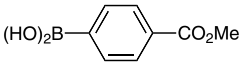
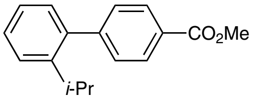
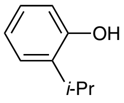
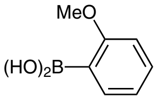
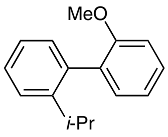
Entry	Phenol **1**	Boronic acid **3**	Time (h)	Product **4**	Yield (%)[b]
1	 **1a**	 **3a**	18	 **4a**	90
2	 **1b**	 **3a**	24	 **4b**	86
3	 **1c**	 **3a**	15	 **4c**	92
4	 **1d**	 **3a**	9	 **4d**	92
5[c]	 **1e**	 **3a**	18	 **4e**	60
6	 **1a**	 **3b**	12	 **4f**	90
7	 **1a**	 **3c**	9	 **4g**	97
8	 **1a**	 **3d**	9	 **4h**	73
9	 **1f**	 **3a**	12	 **4i**	91
10[c]	 **1g**	 **3b**	24	 **4j**	88
11[c]	 **1g**	 **3d**	9	 **4k**	83
12[c]	 **1g**	 **3e**	24	 **4l**	70

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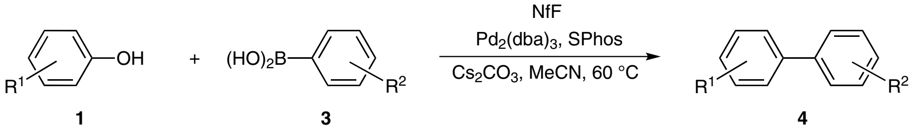
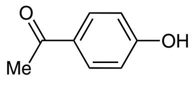
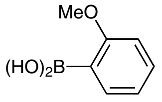
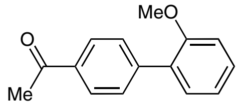
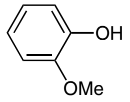
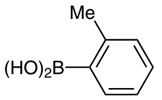
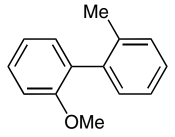
Table 2 Substrate Scope of Suzuki–Miyaura Coupling of Phenols **1** with Arylboronic Acids **3**[a] (continued)



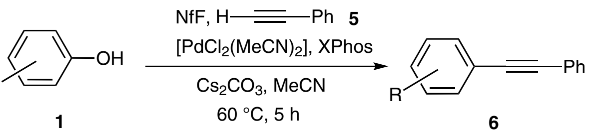
Entry	Phenol **1**	Boronic acid **3**	Time (h)	Product **4**	Yield (%)[b]
13[c]	 **1c**	 **3e**	24	 **4m**	87
14[c]	 **1h**	 **3f**	24	 **4n**	71

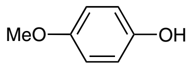
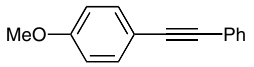
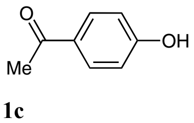
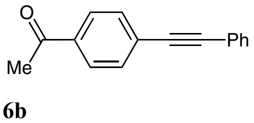
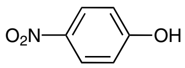
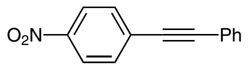
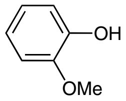
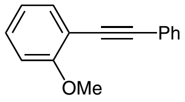
[a] Reaction conditions: **1** (1.0 equiv), **3** (1.5 equiv), NfF (1.5 equiv), Cs_2CO_3 (3.0 equiv), $Pd_2(dba)_3$ (1 mol%), and SPhos (2 mol%) in MeCN (0.5 M) at 60 °C.

[b] Isolated yield of **4**.

[c] Conditions: 3.0 equiv of **3** were used.

Table 3 Sonogashira Coupling of Phenols **1** with Phenylacetylene **5**[a]



Entry	Phenol **1**	Product **6**	Yield (%)[b]
1	 **1b**	 **6a**	79
2	 **1c**	 **6b**	88
3	 **1d**	 **6c**	95
4	 **1h**	 **6d**	80

[a] Reaction conditions: **1** (1.0 equiv), **5** (3.0 equiv), NfF (1.5 equiv), Cs_2CO_3 (3.0 equiv), $[PdCl_2(MeCN)_2]$ (1 mol%), and XPhos (2 mol%) in MeCN (0.5 M) at 60 °C for 5 h.

[b] Isolated yield of **6**.

In conclusion, we have developed the palladium-catalyzed direct cross-coupling reactions of phenols **1** using the air-stable and less expensive NfF. This method does not require the isolation of the intermediary nonaflates **2** and is therefore much more convenient and useful compared to the known traditional methods.[14] Under proper conditions, variously substituted phenols **1a**–**h** were used in a wide range of couplings including the Suzuki–Miyaura, Sonogashira, Stille, and Buchwald–Hartwig reactions.[15]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) Using Ph_3P instead of SPhos, a similar reaction of electron-donating phenol **1b** with **3a** provided only 23% NMR yield of biaryl **4b** accompanied by the formation of nonaflate **2b** (77% NMR yield). Accordingly, we have concluded that SPhos is the better ligand for the one-pot Suzuki–Miyaura coupling, and Ph_3P, which is much less expensive than SPhos, may be an alternative in some cases.

(13) For details, see Supporting Information.

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(15) **General Procedure for the Suzuki–Miyaura Coupling of Phenols 1 (Table 2)**
An oven-dried 10 mL test tube was evacuated and backfilled with nitrogen. The test tube was charged with phenol **1** (0.50 mmol, 1.0 equiv), boronic acid **3** (0.75 mmol, 1.5 equiv or 1.5 mmol, 3.0 equiv), Cs_2CO_3 (1.5 mmol, 3.0 equiv), $Pd_2(dba)_3$ (0.0050 mmol, 1.0 mol%), and SPhos (0.010 mmol, 2.0 mol%). The test tube was sealed with a septum, evacuated, then backfilled with nitrogen (this sequence was repeated three times). To the test tube were added dry MeCN (0.50 M) and NfF (0.75 mmol, 1.5 equiv) via a syringe in this order using a nitrogen balloon, and then the reaction mixture was stirred at 60 °C for several hours. After cooling the reaction mixture to r.t., EtOAc (ca. 1.0 mL) was added. The mixture was filtered through a Celite cake, and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel to give the biaryl **4**.
General Procedure for the Sonogashira Coupling of Phenols 1 (Table 3)
An oven-dried 10 mL test tube was evacuated and backfilled with nitrogen. The test tube was charged with phenol **1** (0.50 mmol, 1.0 equiv), Cs_2CO_3 (1.5 mmol, 3.0 equiv), $[PdCl_2(MeCN)_2]$ (0.0050 mmol, 1.0 mol%), and XPhos (0.010 mmol, 2.0 mol%). The test tube was sealed with a septum, evacuated, then backfilled with nitrogen (this sequence was repeated three times). To the test tube were added dry MeCN (0.50 M), phenylacetylene (**5**, 1.5 mmol, 3.0 equiv), and NfF (0.75 mmol, 1.5 equiv) via a syringe in this order using a nitrogen balloon, and then the reaction mixture was stirred at 60 °C for 5 h. After cooling the reaction mixture to r.t., EtOAc (1 mL) was added. The mixture was filtered through a Celite cake, and the filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel to give the diarylacetylene **6**.
Procedure for the Stille Coupling of 4-Hydroxyacetophenone (1c, Scheme 2)
An oven-dried 10 mL test tube was evacuated and backfilled with argon. The test tube was charged with LiCl (46 mg, 1.5 mmol) and evacuated overnight with heating at 150 °C. After cooling, the test tube was backfilled with argon. The test tube was charged with 4-hydroxyacetophenone (**1c**, 68 mg, 0.50 mmol), Cs_2CO_3 (240 mg, 0.75 mmol), and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.0056 mmol). The test tube was sealed with a septum, evacuated, then backfilled with argon (this sequence was repeated three times). To the test tube were added dry DMF (1.0 mL, 0.50 M), tributylvinyltin (**7**, 61 mg, 0.65 mmol), and NfF (0.13 mL, 0.75 mmol) via a syringe in this order using an argon balloon, then the reaction mixture was stirred at 60 °C for 6 h. After cooling, H_2O was added to the reaction mixture. The reaction mixture was extracted with Et_2O, and the resulting aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with a sat. aq NaCl solution and dried over anhyd Na_2SO_4. The solution was filtered through a glass filter, then the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane–EtOAc = 50:1) to give 4-vinylacetophenone (**8**, 64 mg, 87%) as a colorless solid.
Procedure for the Buchwald–Hartwig Reaction of *p*-Methoxyphenol (1b, Scheme 3)
An oven-dried 10 mL test tube was evacuated and backfilled with argon. The test tube was charged with 4-methoxyphenol (**1b**, 62 mg, 0.50 mmol), aniline (**9**, 61 mg, 0.65

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mmol), Cs_2CO_3 (490 mg, 1.5 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), and XPhos (14 mg, 0.030 mmol). The test tube was sealed with a septum, evacuated, then backfilled with argon (this sequence was repeated three times). To the test tube were added dry toluene (1.0 mL, 0.50 M) and NfF (0.13 mL, 0.75 mmol) via a syringe in this order using an argon balloon, then the reaction mixture was stirred at 105 °C for 15 h. After cooling the reaction mixture to r.t., EtOAc (1 mL) was added. The mixture was filtered through a Celite cake, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane–EtOAc = 10:1) to give 4-methoxydiphenylamine (**10**, 90 mg, 90%) as a colorless solid.

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