Palladium-Catalyzed Regioselective Arylation of Arene C–H Bond Assisted by the Removable 2-Pyridylsulfinyl Group

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Abstract: A palladium-catalyzed arylation of arene C–H bond assisted by a removable 2-pyridylsulfinyl group is described. The reaction employs aryltrifluoroborates as the arylation reagent, leading to the corresponding products in moderate to good yield with broad substrate scope. The directing group can be removed or converted to other useful functionalities, which showcases the potential synthetic application of the methodology.

Key words: C–H bond activation, arylation, aryltrifluoroborate, sulfoxide, palladium catalysis

Biaryls are important structural motifs frequently found in bioactive compounds and functional materials. During the past few decades, extensive efforts have been devoted to the development of constructing biaryl motifs.[1] Compared with the traditional cross-coupling methods (such as Suzuki coupling, Stille coupling, Negishi coupling, and Kumada coupling) employing aryl halides or organometallic derivatives, direct C–H bond arylation provides new opportunities in the synthesis of biaryl compounds.[2] Currently, auxiliary-assisted C–H bond activation has emerged as a powerful tool in organic synthesis.[3] In the majority of arene C–H bond functionalization examples, a directing group has been used as a means of tuning the regioselectivity. Under this speculation, a 2-pyridyl unit,[4] imines,[5] oxymes,[6] carboxylic acids,[7] and *N*-acetyl[8] or *N*-carbamoyl anilines[9] have been successfully applied to achieve arene C–H bond functionalization. However, in some cases, the directing groups are not easily removed, hence compromising the practicality of the reaction. Therefore, the discovery of efficient removable directing groups is highly desirable. Gevorgyan and co-workers reported arene C–H bond transformations directed by pyridyldiisopropylsilyl (PyDipSi) that could be removed easily from the products.[10] Pyridylsulfinyl (PySO) was reported as a removable directing group by the Carretero group[11a] and the Mancheño Group,[11b] respectively. We previously reported a Pd-catalyzed alkenylation and arylation of arenes by the use of 2-pyridyl sulfoxide as directing group.[11c] However, for the arylation, we only got the low regioselectivity and poor activities for limited substrates. Herein, we report an efficient Pd-catalyzed arylation of 2-(arylsulfinyl)pyridines with a variety of organotrifluoroborate substrates as coupling partner.

Organotrifluoroborate is frequently employed as an alternative in cross-coupling reactions due to its advantages such as the stability to air and moisture, easy handling, and the avoidance of byproducts from homocoupling.[12] In consideration of the advantages of organotrifluoroborate, we initiated our investigation with the coupling between 2-(phenylsulfinyl)pyridine (**1a**) and potassium phenyltrifluoroborate (**2a**). When the substrates stirred with 10 mol% of $Pd(OAc)_2$ and two equivalents of Ag_2CO_3 in DCE at 130 °C, the desired product was isolated in 47% yield (Table 1, entry 1). The addition of 1,4-benzoquinone (BQ, Table 1, entry 2) led to the rapid increase of the isolated yield, which was supposed to promote the reductive elimination step.[13] The use of $PdCl_2$ (Table 1, entry 3) and $Pd(MeCN)_2Cl_2$ (Table 1, entry 4) showed relatively lower efficiency, while $Pd(PPh_3)_2Cl_2$ (Table 1, entry 5) and $Pd(PPh_3)_4$ (Table 1, entry 6) were completely ineffective. Screening of the oxidants revealed that Ag_2CO_3 was the most effective oxidant for this reaction (Table 1, entries 7–12). For the choices of the reaction solvents, DCE afforded the highest yield (Table 1, entries 13–18). Lower temperature resulted in the lower yield (Table 1, entry 19). When phenylboronic acid was employed instead of potassium phenyltrifluoroborate, no desired arylation product was detected. The use of less Ag_2CO_3 and $Pd(OAc)_2$ led to the decrease of the yields (Table 1, entry 20).

With the optimal reaction conditions in hand, we examined the substrate scope of aryltrifluoroborates as summarized in Table 2. Among the aryltrifluoroborates, it was found that various kinds of methyl, methoxy, fluoro, cyano, and chloro substituents (Table 2, entries 1–10) were tolerated under the reaction conditions, giving the corresponding products in moderate to good yields. Aryltrifluoroborates with electron-deficient substituents (Table 2, entries 9–10) gave lower yields compared to their electron-rich counterparts. *ortho*-Substituted aryltrifluoroborates (Table 2, entry 11) delivers relatively lower yield compared with its *meta* and *para* analogues due to the steric hindrance.

The substrate scope of 2-(arylsulfinyl)pyridine was evaluated with potassium phenyltrifluoroborate (**2a**) as presented in Table 3. Both electron-rich and electron-deficient 2-(arylsulfinyl)pyridines were accommodated with good efficiency (Table 3, entries 1–3). The *ortho*

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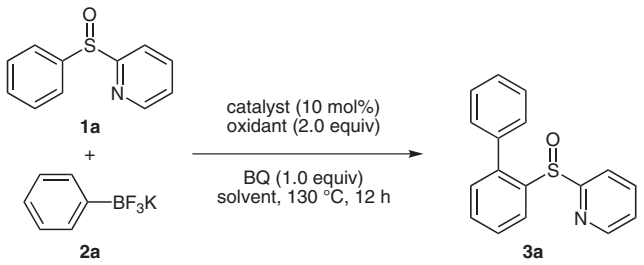
Table 1 Optimization of Reaction Conditions[a,b]

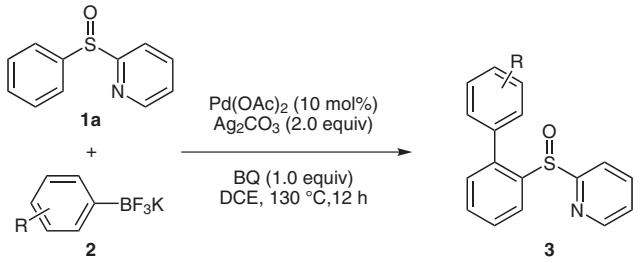


Entry	Catalyst	Oxidant	Solvent	Yield (%)
1	$Pd(OAc)_2$	Ag_2CO_3	DCE	47[c]
2	$Pd(OAc)_2$	Ag_2CO_3	DCE	83
3	$PdCl_2$	Ag_2CO_3	DCE	34
4	$Pd(MeCN)_2Cl_2$	Ag_2CO_3	DCE	19
5	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	DCE	n.d.
6	$Pd(PPh_3)_4$	Ag_2CO_3	DCE	n.d.
7	$Pd(OAc)_2$	AgOAc	DCE	69
8	$Pd(OAc)_2$	Ag_2O	DCE	78
9	$Pd(OAc)_2$	$AgNO_3$	DCE	36
10	$Pd(OAc)_2$	$Cu(OAc)_2$	DCE	27
11	$Pd(OAc)_2$	$PhI(OAc)_2$	DCE	38
12	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	45
13	$Pd(OAc)_2$	Ag_2CO_3	1,4-dioxane	46
14	$Pd(OAc)_2$	Ag_2CO_3	DMF	34
15	$Pd(OAc)_2$	Ag_2CO_3	DMSO	n.d.
16	$Pd(OAc)_2$	Ag_2CO_3	toluene	76
17	$Pd(OAc)_2$	Ag_2CO_3	xylene	41
18	$Pd(OAc)_2$	Ag_2CO_3	anisole	35
19	$Pd(OAc)_2$	Ag_2CO_3	DCE	74[d]
20	$Pd(OAc)_2$	Ag_2CO_3	DCE	54[e]

[a] Reaction conditions: 2-(phenylsulfinyl)pyridine (0.2 mmol), potassium phenyltrifluoroborate (0.4 mmol), palladium catalyst (0.02 mmol), BQ (0.2 mmol), oxidant (0.4 mmol) stirred in solvent (1.5 mL) at 130 °C for 12 h.
[b] Isolated yield of **3a**.
[c] In the absence of BQ.
[d] The reaction was conducted at 120 °C.
[e] Conditions: 1 equiv of Ag_2CO_3 and 5 mol% $Pd(OAc)_2$ were used.

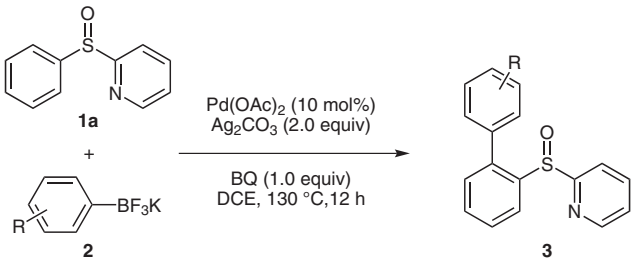
substituent gave the arylation product in 82% yield (Table 3, entry 4). Notably, *meta*-substituted substrate (Table 3, entry 5) reacted regioselectively at the sterically less hindered C–H site. The arylation product was obtained as a mixture of regioisomers when 2-(naphthalen-2-ylsulfinyl)pyridine (Table 3, entry 6) was used as a substrate, which illustrated that proper steric hindrance is crucial for high regioselectivity.

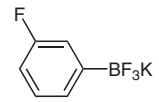
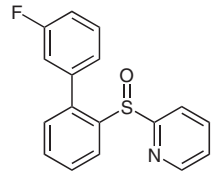
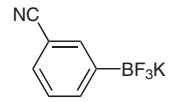
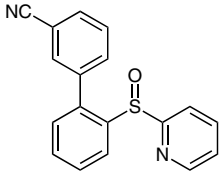
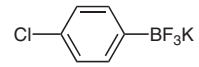
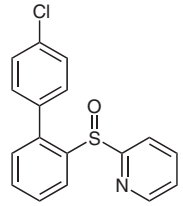
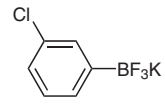
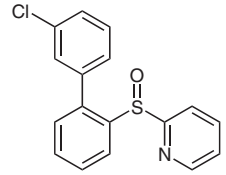
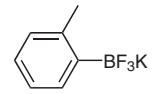
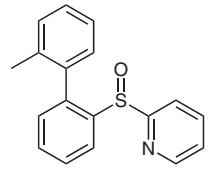
Table 2 Reaction of 2-(Phenylsulfinyl)pyridine with Different Organotrifluoroborates[a,b]



Entry	2	Product 3	Yield (%)
1	**2a**	**3a**	83
2	**2b**	**3b**	72
3	**2c**	**3c**	86
4	**2d**	**3d**	71
5	**2e**	**3e**	74
6	**2f**	**3f**	68

Table 2 Reaction of 2-(Phenylsulfinyl)pyridine with Different Organotrifluoroborates[a,b] (continued)

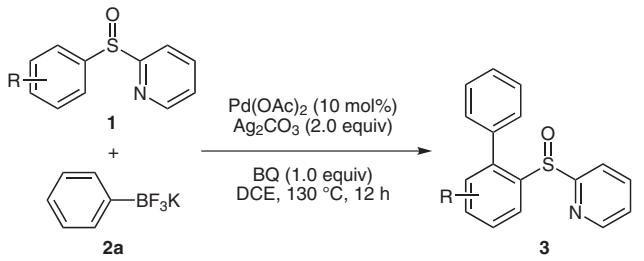


Entry	2	Product 3	Yield (%)
7	 **2g**	 **3g**	61
8	 **2h**	 **3h**	78
9	 **2i**	 **3i**	43
10	 **2j**	 **3j**	48
11	 **2k**	 **3k**	44[c]

[a] Reaction conditions: 2-(phenylsulfinyl)pyridine (0.2 mmol), organotrifluoroborate (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), BQ (0.2 mmol), Ag_2CO_3 (0.4 mmol) stirred in DCE (1.5 mL) at 130 °C for 12 h.
[b] Isolated yield.
[c] Obtained as a 1:1 mixture of diastereoisomers.

On the basis of previous studies[11] and our experimental results, a plausible mechanism of the reaction is proposed as shown in Scheme 1. The electrophilic palladation first occurs under the aid of the pyridine group at the *ortho* site of the substrates, and the subsequent deprotonation leads to the formation of the intermediate **A**. Transmetalation between aryltrifluoroborates and the intermediate **A** affords the intermediate **B**,[12f,14] which undergoes reductive elimination by librating the arylation product and Pd(0), with the acceleration of BQ.[13] Oxidation of Pd(0) by Ag_2CO_3 regenerates Pd(II) for the next catalytic cycle.

Table 3 Reaction of 2-(Arylsulfinyl)pyridine with Different Phenyltrifluoroborates[a,b]



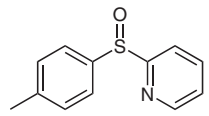
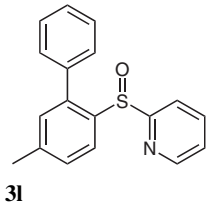
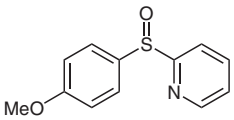
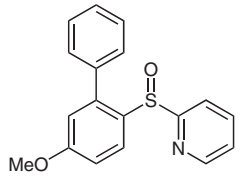
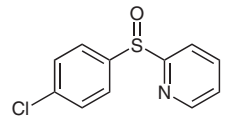
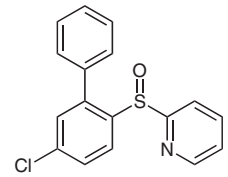
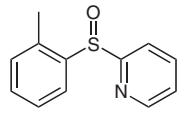
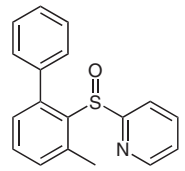
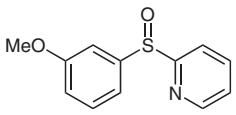
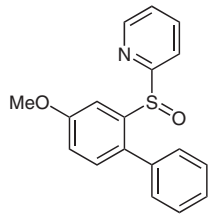
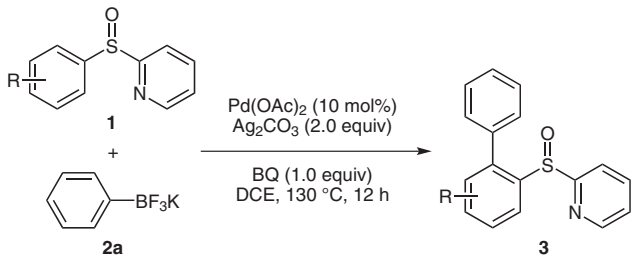
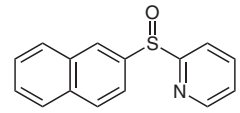
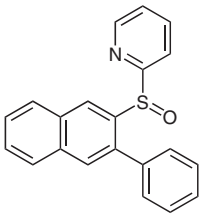
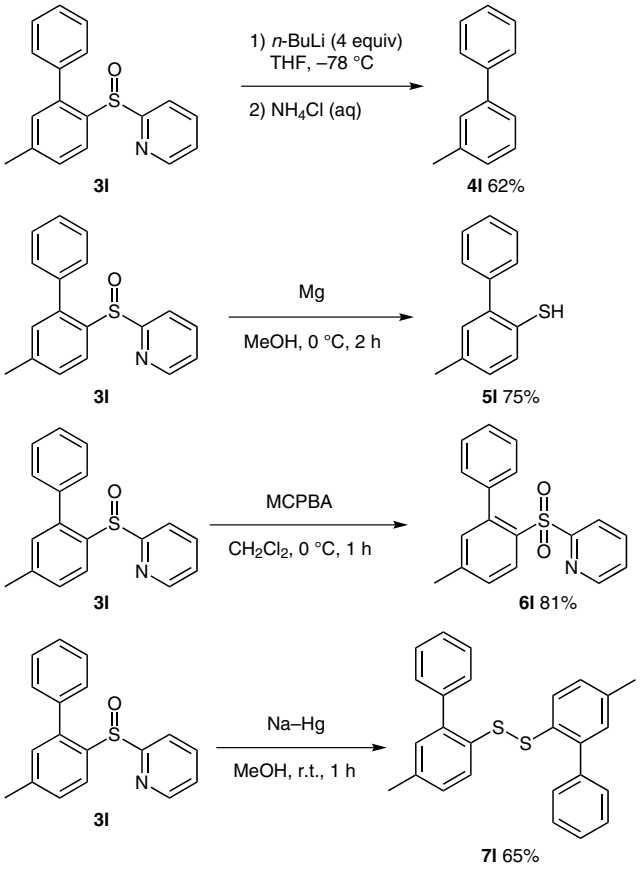
Entry	1	Product 3	Yield (%)
1	 **1b**	 **3l**	91
2	 **1c**	 **3m**	68
3	 **1d**	 **3n**	62
4	 **1e**	 **3o**	82
5	 **1f**	 **3p**	70

Table 3 Reaction of 2-(Arylsulfinyl)pyridine with Different Phenyltrifluoroborates[a,b] (continued)



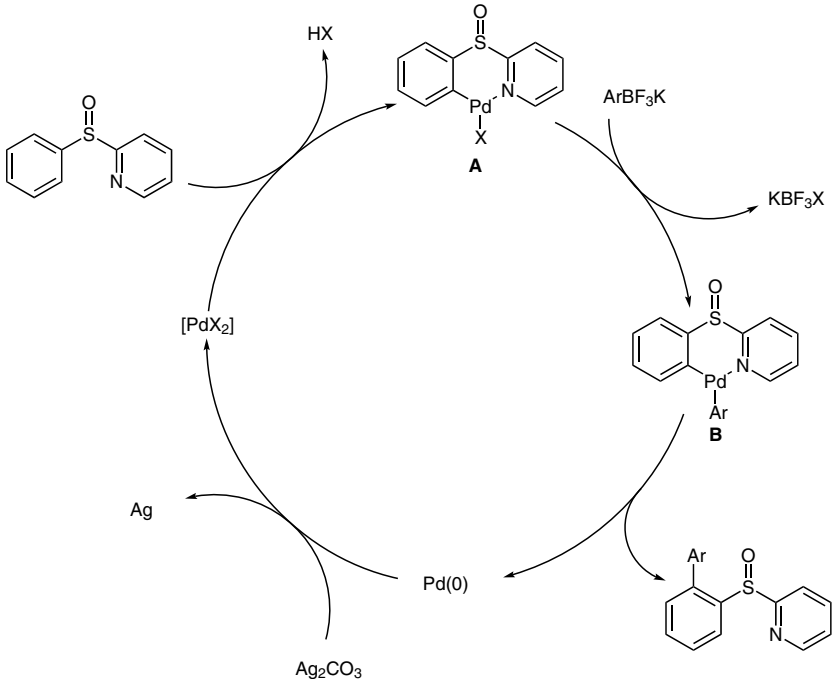
Entry	1	Product 3	Yield (%)
6	 1g	 3q	61[c]

[a] Reaction conditions: 2-(arylsulfinyl)pyridine (0.2 mmol), potassium phenyltrifluoroborate (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), BQ (0.2 mmol), Ag_2CO_3 (0.4 mmol) stirred in DCE (1.5 mL) at 130 °C for 12 h.
[b] Isolated yield.
[c] Obtained as a 42:58 mixture of regioisomers by GC–MS.



Scheme 2 Transformations and removal of the directing group

In order to demonstrate the potential synthetic application of the methodology, we explored further transformations of the arylation product (Scheme 2). Firstly, the (2-pyridyl)sulfinyl group could be easily removed by the treatment of the corresponding arylation product with *n*-BuLi in 62% yield.[11,15] Treatment of the product with Mg affords the thiol **5l** in 75% yield.[11a] The sulfoxide can be oxidized to afford the sulfone product **6l** in 81% yield. In the presence of sodium amalgam, disulfide **7l** can be obtained in 65% yield.[11c]



Scheme 1 Plausible mechanism

In summary, we have successfully developed an efficient palladium-catalyzed arylation of arene C–H bond using 2-pyridyl sulfoxide as a removable directing group. This protocol expands the scope of the arylation reactions by the use of aryltrifluoroborates as coupling partners and demonstrates the excellent regioselectivity. The directing group has been removed or converted to other useful functionalities to prove the potential synthetic usefulness of the methodology.

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

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