# **Thioethers as Directing Group for the Palladium-Catalyzed Direct Arylation of Arenes**

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**Abstract:** Thioethers have proven to be efficient directing groups for the arylation of arenes under palladium catalysis. The thioether group can be readily removed or converted to other functional groups. Kinetic isotopic effect studies reveal that the C–H cleavage of arenes might be the turnover-limiting step.

**Keywords:** arylation; C–H bond activation; palladium; potassium organotrifluoroborates; thioethers

Biaryls are important building blocks of natural products, pharmaceuticals, functionalized materials, and asymmetric catalysts.<sup>[1]</sup> Consequently, the development of straightforward and environment-friendly methods for the preparation of biaryls has attracted substantial interest. The famous cross-coupling reactions, i.e., Suzuki, Stille, Negishi, and Kumada reactions, have become reliable tools for the construction of biaryls.<sup>[2]</sup> However, these methods usually require the prefunctionalized aromatic substrates (aryl halides or organometallic derivatives) as starting materials. In recent years, direct C-H arylation has been intensively investigated owing to its atom- and step-economic advantages.<sup>[3]</sup> In particular, chelation-assisted C-H arvlation has emerged as a powerful method for the effective and regioselective construction of biaryls. Previous studies have demonstrated that ketones,<sup>[4]</sup> amides,<sup>[5]</sup> imines,<sup>[6]</sup> pyridyl,<sup>[7]</sup> nitriles<sup>[8]</sup> and carboxylic acids<sup>[9]</sup> could serve as directing groups in the arylation of arenes. In these transformations, the directing groups in some cases are irremovable and recalcitrant to undergo further synthetic elaboration, and hence limited their wider applications.

The thioether is one of the most important functional groups and exists in many bioactive compounds and natural products.<sup>[10]</sup> It has also been used as coordination group with various metals in many useful catalysts.<sup>[11]</sup> However, functionalization of thioether derivatives using thioether as directing group by C–H activation has rarely been reported.<sup>[12]</sup> Recently, our group explored the utilization of the thioether group as directing group for the catalytic *ortho*-alkenylation of arene C–H bonds.<sup>[13]</sup> It was established that thioethers could functionalize as directing group for the C–H activation in palladium catalysis. Herein we would like to report an efficient Pd-catalyzed arylation of arenes with a variety of potassium aryltrifluoroborates using thioethers as directing group. The thioether group could be easily removed or transformed into other useful functionalities.

We envisaged that the arylation, one of the most important transformations in organic synthesis, could also occur through the thioether-assisted activation of C-H bond in the presence of a palladium catalyst. Accordingly, arylboronic acids,<sup>[14]</sup> which are widely used coupling partners for aryl-carbon bonds, were first tested. However, no desired product was detected and only homocoupling products of the arylboronic acid were obtained. Organotrifluoroborate salts have been well studied by Molander and others as an alternative to organoboronic acids in the Suzuki reaction and other coupling reactions.<sup>[15]</sup> These salts can be readily prepared through a variety of one-pot synthetic routes from readily available starting materials.<sup>[16]</sup> By taking advantages of the attractive features of organotrifluoroborate salts, we examined the reaction of potassium 4-methoxyphenyltrifluoroborate (2a) with (3-methylbenzyl)(p-tolyl)sulfane (1a) in the presence of  $Pd(OAc)_2$  (10 mol%) and  $Ag_2CO_3$ (3 equiv.) at 130°C in DCE. To our delight, the desired product was isolated in 40% yield (Table 1, entry 1). The homocoupling product from potassium phenyltrifluoroborate was not observed. Further optimization revealed that the addition of 0.3 equiv. 1,4benzoquinone (BQ) resulted in a dramatic improvement of the reaction to afford a 73% yield (Table 1,

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Table 1. Optimization of reaction conditions.<sup>[a]</sup>



	2			[]
1	$Pd(OAc)_2$	Ag <sub>2</sub> CO <sub>3</sub>	DCE	40 <sup>[c]</sup>
2	$Pd(OAc)_2$	$Ag_2CO_3$	DCE	73
3	PdCl <sub>2</sub>	$Ag_2CO_3$	DCE	21
4	$Pd(PPh_3)_2Cl_2$	$Ag_2CO_3$	DCE	10
5	$Pd(PPh_3)_4$	$Ag_2CO_3$	DCE	N.R.
6	$Pd(OAc)_2$	AgOAc	DCE	55
7	$Pd(OAc)_2$	AgOTFA	DCE	49
8	$Pd(OAc)_2$	$Ag_2O$	DCE	31
9	$Pd(OAc)_2$	$Ag_2CO_3$	toluene	21
10	$Pd(OAc)_2$	$Ag_2CO_3$	xylene	22
11	$Pd(OAc)_2$	$Ag_2CO_3$	1,4-dioxane	12
12	$Pd(OAc)_2$	$Ag_2CO_3$	<i>i</i> -PrOH	N.R.
13	$Pd(OAc)_2$	$Ag_2CO_3$	DMF	N.R.
14	$Pd(OAc)_2$	$Ag_2CO_3$	DMSO	N.R.
15	$Pd(OAc)_{2}$	Ag <sub>2</sub> CO <sub>2</sub>	DCE	29 <sup>[d]</sup>

<sup>[a]</sup> Reaction conditions: (3-methylbenzyl)(p-tolyl)sulfane 1a (0.2 mmol), potassium aryltrifluoroborate 2a (0.6 mmol), palladium catalyst (0.02 mmol), BQ (0.06 mmol), oxidant (0.6 mmol), solvent (2 mL) , 130 °C , 24 h.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> In the absence of BQ.

<sup>[d]</sup> The reaction was conducted at 110°C.

entry 2).<sup>[17]</sup> Other palladium catalysts, including PdCl<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, showed relatively lower efficiency (Table 1, entries 3 and 4), and  $Pd(PPh_3)_4$  was completely inactive (Table 1, entry 5). Among the oxidants examined, Ag<sub>2</sub>CO<sub>3</sub> gave the highest yield (Table 1, entry 2). A comparable reaction efficiency was presented by AgOAc, while AgOTFA and Ag<sub>2</sub>O showed poor reactivity (Table 1, entries 6-8). The solvent played an important role in this transformation. Dichloroethane was the best solvent for this reaction. Other solvents, such as toluene, xylene, and dioxide, led to poor yields (Table 1, entries 9-11). The reaction did not occur in *i*-PrOH, DMF and DMSO (Table 1, entries 12-14). The temperature was found to influence the reactivity. For example, lowering the temperature to 110°C caused the yield to decrease to 29% (Table 1, entry 15).

Next, we turned our attention to investigate the scope of the potassium aryltrifluoroborates as shown in Table 2. In most cases, good results were obtained for the potassium trifluoroarylborates with an electron-donating group in the aromatic ring (Table 2, entries 1–6). Potassium aryltrifluroborates with *ortho* 

**Table 2.** Reaction of (3-methylbenzyl)(*p*-tolyl)sulfane with potassium aryltrifluoroborates.<sup>[a]</sup>



#### Table 2. (Continued)



<sup>[a]</sup> Reaction conditions: thioether arene **1a** (0.2 mmol), potassium aryltrifluoroborate **2** (0.6 mmol),  $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), BQ (6.5 mg, 0.06 mmol),  $Ag_2CO_3$ (164.4 mg, 0.6 mmol), DCE (2 mL), 130 °C, 24 h.

<sup>[b]</sup> Isolated yield.

substitutents could not participate the reaction (Table 2, entry 7), illustrating that the steric hindrance played a role in the reaction. The presence of electron-withdrawing groups such as Cl, F, and CN in the aromatic ring of aryltrifluoroborate salts led to lower efficiency (Table 2, entries 8–10). Potassium 2-naph-thalenyltrifluoroborate underwent the reaction smoothly and a 53% yield was afforded (Table 2, entry 11). The super reactivity of potassium aryltrifluoroborates might be rationalized by the greater nucleophilicity of potassium trifluoroborates over the corresponding boronic acids.<sup>[9c,15c]</sup>

The substituent groups on the thioether arenes influenced the direct arylation reactions as summarized in Table 3. Arenes containing electron-withdrawing substituents exhibited lower yields in the arylation than their electron-rich counterparts. For example, the yields of Cl- and F-substituted arenes were considerably depressed in contrast to those of Me- and MeO-substituted arenes (Table 3, entries 1–7). In the case of benzyl(*p*-tolyl)sulfane **1i**, the diarylated product was isolated in 12% yield, which led to a lower yield of **3s**. It should be noted that various thioethers were well tolerated and showed the good reactivity to afford the corresponding arylated products (Table 3, entries 9 and 10).

To gain insight into the reaction mechanism, an intermolecular isotope kinetic experiment was carried out. Benzyl(*p*-tolyl)sulfane **1i** and its deuterated analogue **1i**- $d_5$  were equivalently subjected to the reaction (Scheme 1). A significant kinetic isotope effect (KIE) of 2.7 was observed, indicated that the C–H cleavage might be involved in the rate-determining step in this new catalytic system.<sup>[20]</sup>

In order to demonstrate the potential synthetic application of the new reaction, we explored transformations of the arylated products with the model prod**Table 3.** Reaction of thioethers with potassium 4-methoxy-phenyltrifluoroborate.<sup>[a]</sup>



Table 3. (Continued)



- <sup>[a]</sup> Reaction conditions: (3-methylbenzyl)(p-tolyl)sulfane **1** (0.2 mmol), potassium aryltrifluoroborate **2a** (0.6 mmol), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol), BQ (6.5 mg, 0.06 mmol), Ag<sub>2</sub>CO<sub>3</sub> (164.4 mg, 0.6 mmol), DCE (2 mL), 130 °C, 24 h.
- <sup>[b]</sup> Isolated yield.
- <sup>[c]</sup> 12% of diarylation product was also isolated.

uct 3c (Scheme 2). The cleavage of the phenylthio group was achieved under reductive conditions using Raney Ni in the presence of hydrazine hydrate to obtain the corresponding arylation product 5c in 73% yield. By regulating the dosage of the oxidant *m*-CPBA and reaction time, the thioether could be oxidized to afford the sulfone 6c or sulfoxide 7c in good yields.

In principle, two different reaction pathways can be envisioned for the initial arylation: (i) the electrophilic palladation and subsequent arylation;<sup>[18]</sup> (ii) directed  $C(sp^2)$ -H activation and subsequent arylation.<sup>[19]</sup> In our experiment, the electron-rich thioether arenes showed higher reactivity than the electron-difficient



Scheme 1. Kinetic isotope experiment.

arenes, which is consistent with the electrophilic palladation mechanism.<sup>[18]</sup> According to our previous studies<sup>[13]</sup> and the experimental results, a plausible reaction mechanism is proposed for this new arylation process as shown in Scheme 3. The electrophilic palladation and deprotonation occurs at the *ortho*-position of thioether arene to give the intermediate **A**, which reacts with the potassium aryltrifluoroborate to afford the (aryl)(aryl)palladium(II) species **B**. The subsequent reductive elimination liberates the biaryl product with the formation of Pd(0), which is oxidized by Ag<sub>2</sub>CO<sub>3</sub> to regenerate the Pd(II) for the next catalytic cycle. Further research is required to elucidate the detailed reaction mechanism.

In summary, we have developed an efficient protocol for regioselective arylation of arenes *via* the thioether-assisted C–H bond activation by the palladium catalysis. Potassium aryltrifluoroborate were proven



Scheme 3. Proposed mechanism.



Scheme 2. Removal and transformation of thioethers.

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to be the suitable coupling partners. This transformation represents a rare example of the application of thioether as the directing group, which allows an efficient synthesis of a variety of biaryls and sulfur-containing compounds. Further development of other C– H functionalizations by the use of thioether as directing group is underway in our laboratories.

## **Experimental Section**

### **Typical Procedure**

To a 25-mL sealable tube containing a magnetic stir bar in air, were added (3-methylbenzyl)(*p*-tolyl)sulfane **1a** (27.4 mg, 0.2 mmol), potassium 4-methoxyphenyltrifluoroborate **2a** (128.4 mg, 0.6 mmol), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol), benzoquinone (6.5 mg, 0.06 mmol), Ag<sub>2</sub>CO<sub>3</sub> (164.4 mg, 0.6 mmol) and DCE (2 mL). The tube was sealed with a Teflon-lined cap, and the reaction mixture was stirred at 130 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The reaction mixture was filtered through a plug of Celite and the residue was washed with ethyl acetate (2×20 mL). The combined organic phases was concentrated under vacuum and the residue was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether=1:100, v/v) to afford the desired product; yield: 73%.

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