

# Research Article **Palladium-Catalyzed C(sp<sup>3</sup>)-H Arylation of Benzo[b]thiophen-3(2H)-one 1,1-Dioxide**

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A new concise synthesis route of 2-phenylbenzo[b]thiophen-3(2H)-one 1,1-dioxide from benzo[b]thiophen-3(2H)-one 1,1-dioxide was developed using palladium-catalyzed  $C(sp^3)$ -H arylation. Compared with the traditional route, this protocol can effectively save many steps and combine with the current research hotspot,  $C(sp^3)$ -H activation. Moreover, this catalytic system is easy to operate and a good yield can be achieved.

# 1. Introduction

In the past few decades, transition metal-catalyzed C-H activation has developed into one of the most powerful tools in organic synthesis, in contrast to traditional coupling reaction, which has the advantages of no preactivation of substrates and excellent atom economy, demonstrating the future direction of organic synthesis methodology. The activation of active C-H bond has been well developed till now. Besides, direct arylation of  $\alpha$ -functionalized carbonyl compounds has been well developed in recent years [1]. Arylated benzo[b]thiophen-3(2H)-one 1,1-dioxide is a kind of important biological active intermediates, which has antiinflammation and anticoagulation effects [2, 3]. For these compounds, the traditional synthesis methods [4, 5] are very complex which need many steps to get the target products, so that we decided to find a new way of shortening the reaction steps (Scheme 1).

The skeleton of  $\beta$ -ketosulfone is a useful building block in synthetic chemistry [6]. The related derivatives are useful precursors for functional group transformations, which can exhibit some biological activities for medicinal application [7]. However, there are only few reports about  $\alpha$ -arylation of  $\beta$ -ketosulfones. In 2002, Kashin and coworkers found the palladium-catalyzed arylation of sulfonyl CH-acids, but only one case was reported with lower yield [8], involving the  $S_NAr$  arylation. In 2015, Chang and coworkers reported the palladium-mediated  $\alpha$ -arylation of  $\beta$ -ketosulfones with aryl iodides in the presence of strong base (LiTMP), Lewis acid (ZnF<sub>2</sub>), and complicated phosphine ligand (RuPhos) [9]. Moreover, the generation of six-member ring intermediate with the auxiliary of Lewis acid is possibly necessary for this type reaction [10]. However, the substrate in our work is a cyclic compound which is unable to form a six-member ring intermediate with Lewis acid. Herein, we describe the palladium-catalyzed C(sp<sup>3</sup>)-H arylation of benzo[b]thiophen-3(2H)-one 1,1-dioxide, which has not been reported to the best of our knowledge.

#### 2. Results and Discussion

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, and the experimental conclusions that can be drawn.

2.1. Optimization of Phosphine Ligands. Initially, we carried out the reaction in toluene at 110°C, in the presence of 10 mol% of Pd(OAc)<sub>2</sub>, 20 mol% PCy<sub>3</sub>·HBF<sub>4</sub>(L1), and KO<sup>t</sup>Bu,



SCHEME 1: Traditional route vs. our route.

affording **1c** in 60% yield (Table 1, entry 1). Since phosphine ligands are very important for the stability of catalyst precursors, we first screened different kinds of phosphine ligands (Scheme 2). The results are shown in Table 1.

In this reaction, by testing a series of sterically and electronically diverse mono- and bidentate ligands, we found that the performance of the monodentate phosphine ligands is relatively better than that of the bidentate phosphine ligands. The electron-rich monodentate phosphine ligand had better influence on this reaction (Table 1, entry 1 vs. Table 1, entry 2). In contrast, when we tried to increase the electron density on phosphine, the yield decreased to 38% (Table 1, entry 2 vs. Table 1, entry 8). Moreover, the sterically hindered monodentate phosphine ligand afforded **1c** in a lower yield (Table 1, entry 1 vs. Table 1, entry 7). In the literature, we found that chiral C-H activation is a challenging study, so we investigated the effect of racemic chiral phosphine ligands on this reaction. Unfortunately, only low yields were achieved (Table 1, entry 4, 47%, and Table 1, entry 9, 17%). **1c** was not detected



TABLE 1: Optimization of phosphine ligands.

<sup>1</sup>Reaction conditions: 10 mol% of Pd(OAc)<sub>2</sub>, 20 mol% of ligand, 0.25 mmol of **1a**, 0.5 mmol of **1b**, 0.75 mmol of KO'Bu, and 1 mL of toluene, 110°C, 24 h. <sup>2</sup>GC yield.



SCHEME 2: Phosphine ligands.

using **L10** as a ligand, but carbazole was found in reaction system which indicated that P-N cleavage of **L10** happened. Without the addition of phosphine ligands, the target

product 1c was not obtained (Table 1, entry 11), demonstrating that phosphine ligands were indispensable in this reaction.

Entry <sup>1</sup>	Solvents		Temp (°C)	Bases	Yield (%) <sup>2</sup>
	(	Br	Pd(OAc) <sub>2</sub> base Solvent temp L1		
	1a	1b		1c	
1	Dioxane		100	$KO^{t}Bu$	59
2	THF		60	$KO^{t}Bu$	58
3	MTBE		50	KO <sup>t</sup> Bu	NR
4	Anisole		150	KO <sup>t</sup> Bu	28
5	DME		80	KO <sup>t</sup> Bu	NR
6	<sup>t</sup> BuOH		80	KO <sup>t</sup> Bu	NR
7	DMAc		140	$KO^{t}Bu$	62
8	DMC		90	KO <sup>t</sup> Bu	NR
9	NMP		140	$KO^{t}Bu$	65
10	NMP		140	K <sub>3</sub> PO <sub>4</sub>	$83(73)^3$
11	NMP		140	LiO <sup>t</sup> Bu	46
12	NMP		140	KOAc	NR
13	Toluene		110	K <sub>3</sub> PO <sub>4</sub>	$73 (69)^3$

TABLE 2: Optimization of solvents and bases.

<sup>1</sup>Reaction conditions: 10 mol% of Pd(OAc)<sub>2</sub>, 20 mol% of L1, 0.25 mmol of 1a, 0.5 mmol of 1b, 0.75 mmol of bases, and 1 mL of solvent, 24 h. <sup>2</sup>GC yield. <sup>3</sup>Isolated yield in parentheses.

2.2. Optimization of Solvents and Bases. Due to the great influence of the solvents and bases on the reaction, we carried out a series of screenings for the solvents and bases to further improve the yield, which are shown in Table 2. A moderate yield (59%) can be obtained using dioxane as the solvent (Table 2, entry 1). Then a series of ethers were screened. We found that the yield in THF was 58% (Table 2, entry 2), but the yields in the other ether are low (Table 2, entries 3, 4, and 5). After that, the polar aprotic solvents were screened, and the common high boiling point solvents were selected and tested. To our delight, when NMP was used as the solvent, the yield was increased to 65% (Table 2, entry 9). In this type of reaction, the pK<sub>a</sub> of the substrate has a great influence on the reaction, so the kind of base used is critical to the process of deprotonation to form the carbon anion intermediate [11]. Therefore, we screened the bases. A moderate yield was obtained using LiO<sup>t</sup>Bu as a base (Table 2, entry 11), but a large amount of bromobenzene was converted into biphenyl through dehalogenated coupling. When K<sub>3</sub>PO<sub>4</sub>, an inorganic salt, was used as a base, a good yield of 83% was achieved (Table 2, entry 10). However, the product was not detected while using KOAc as a base, probably because the basicity KOAc is too weak to complete the deprotonation process (Table 2, entry 12). It is generally believed that polar aprotic solvents and higher temperature may increase the possibility of aldol condensation of substrate. So we tried to replace the solvent with toluene, and a good result was also obtained (Table 2, entry 13).

Consequently, the optimized reaction conditions were 10 mol% of Pd(OAc)<sub>2</sub>, 20 mol% of L1, 0.75 mmol of K<sub>3</sub>PO<sub>4</sub>, and 1 mL of NMP or toluene.

2.3. The Scope of Substrates. Under the optimized conditions, we tested several kinds of aryl bromides, affording the target products (Table 3). Substrates with electron-donating group had a positive effect on this reaction. The yields were improved to 75% and 71%, respectively (Table 3, entries 1 and 2). Conversely, the yields were obviously decreased by the substrates with electron-withdrawing groups, such as –Cl and –CN (Table 3, entries 4 and 5). Unfortunately, aryl bromide with large steric hindrance cannot be converted into target product (Table 3, entry 3). Moreover, heteroaromatic bromide was incompatible in our system (Table 3, entry 6).

2.4. Proposed Mechanism. To account for these outcomes, a possible catalytic cycle (Scheme 3) was proposed based on our experiments and the previous reports [11, 12]. This reaction is likely to proceed via a deprotonative cross-coupling procedure [13].

Oxidative addition of the Pd(0) with bromobenzene affords the Pd(II) organometallic intermediate 3. Deprotonation of 1a and ligand substitution of the bromide provide 2. Finally, reductive elimination of 2 affords target product 1c and regenerates the Pd(0) catalyst. In general, reductive elimination is not the rate-limiting step of coupling reaction. However, in this reaction, we believe



<sup>1</sup>Reaction conditions: 10 mol% of Pd(OAc)<sub>2</sub>, 20 mol% of L1, 0.25 mmol of 1a, 0.5 mmol of b, 0.75 mmol of bases, and 1 mL of solvent, 24 h. <sup>2</sup>Isolated yield.



SCHEME 3: Proposed mechanism.

that the reductive elimination is much slower to form the aryl-alkyl bond from an arylmetal alkyl intermediate when the alkyl group contains strong electron-withdrawing groups on the  $\alpha$  position [14].

#### 3. Experimental

All reactions were carried out in a dried Schlenk tube under a nitrogen atmosphere. Unless otherwise indicated, reagents obtained from commercial sources were used without further purification. DMAc, anisole, and NMP were dried and distilled under reduced pressure and stored on molecular sieves (4 Å). Dimethyl carbonate (DMC) was dried, distilled, and stored on molecular sieves (4 Å). THF, toluene, and dioxane were dried and distilled with sodium and diphenylketone acts as an indicator. Gas chromatography is Aglient GC 6890 N and the column is SE-30 ( $30 \text{ m} \times 0.32 \text{ mm} \times 0.25 \mu\text{m}$ ). NMR spectra were recorded on Bruker Avance II (400 MHz). HR-ESIMS spectra were recorded using a commercial apparatus.

3.1. Synthesis of Benzo[b]thiophen-3(2H)-one 1,1-Dioxide (1a). Ethyl benzoylacetate (2.5 mL, 14.6 mmol) was slowly added dropwise into excess of 50% oleum at 0°C. The mixture was stirred for 30 min and poured into 50 mL ice-water mixture and stirred. The yellow precipitate was filtered and recrystallized with ethanol. White crystal was achieved and the yield was 50%. The above crystals were dissolved in 10 mL 20% H<sub>2</sub>SO<sub>4</sub> and stirred for 10 min at 0°C. Then 10 mL ethanol was added and refluxed. The reaction progress was monitored by TLC. After the reaction was completed, we cooled the mixture in the refrigerator until the crystals were separated out. The crystals were then filtered and washed with a small amount of distilled water. Finally, the pale yellow crystals were obtained by recrystallization with ethanol, and the yield of 1a was 70%. Benzo[b]thiophen-3(2H)-one 1,1-dioxide:  $C_8H_6O_3S$ , pale yellow crystal, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 8.06 - 7.99$  (m, 2H), 7.96 (td, J = 7.6, 1.0 Hz, 1H), 7.87-7.81 (m, 1H), 4.10 (s, 2H). ESI-HRMS: calcd for  $C_8H_6NaO_3S^+([M + Na^+])$  204.9935, found 204.9943.

3.2. Typical Procedure for the Palladium-Catalyzed  $C(sp^3)$ -H Arylation of Benzo[b]thiophen-3(2H)-one 1,1-Dioxide (1a).

Pd(OAc)<sub>2</sub> (0.025 mmol, 5.6 mg), PCy·HBF<sub>4</sub> (0.05 mmol, 18.5 mg), **1a** (0.25 mmol, 45.5 mg), and KO<sup>t</sup>Bu (0.75 mmol, 84 mg) were added to a Schlenk flask. And the mixture was dissolved in 1 mL of toluene under a nitrogen atmosphere. The reaction mixture was stirred at 110°C for 24 h. Then, ethyl acetate was used to dissolve the mixture as much as possible (except for inorganic salt). Celatom was used to filter undissolved substance. After this, the solvent was evaporated under vacuum and the mixture was analyzed by GC or purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 3:1) to afford product 1c as a pale yellow solid. 2-phenylbenzo[b]thiophen-3(2H)one 1,1-dioxide: C<sub>14</sub>H<sub>10</sub>O<sub>3</sub>S, pale yellow solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.10 (dd, J = 15.5, 7.8 Hz, 2H), 8.00 (t, J = 7.4 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.28 (dd, *J* = 6.4, 3.1 Hz, 2H), 5.17 (s, 1H). ESI-HRMS: calcd for  $C_{14}H_{10}NaO_3S^+([M + Na^+])$  281.0248, found 281.0255.

3.3. Characterization of Products. 2-(4-Methoxyphenyl)benzo [b]thiophen-3(2H)-one 1,1-dioxide (**2c**):  $C_{15}H_{12}O_4S$ , pale yellow solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.15 (dd, J = 15.3, 7.7 Hz, 2H), 8.03 (t, J = 7.1 Hz, 1H), 7.93 (t, J = 7.4 Hz, 1H), 7.15 – 7.01 (m, 2H), 6.85 (dd, J = 6.3, 3.2 Hz, 2H), 5.33 (s, 1H), 3.73 (s, 3H). ESI-HRMS: calcd for  $C_{15}H_{12}NaO_4S^+([M + Na^+])$  311.0354, found 311.0355.

2-(*p*-Tolyl)benzo[b]thiophen-3(2H)-one 1,1-dioxide (**3c**):  $C_{15}H_{12}O_3S$ , pale yellow solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 8.09$  (dd, J = 15.4, 7.7 Hz, 2H), 8.01 (t, J = 7.2 Hz, 1H), 7.92 (t, J = 7.5 Hz, 1H), 7.45 – 7.34 (m, 2H), 7.12 (dd, J = 6.4, 3.3 Hz, 2H), 5.21 (s, 1H), 2.26 (s, 3H). ESI-HRMS: calcd for  $C_{15}H_{12}NaO_3S^+([M + Na^+])$  295.0405, found 295.0409.

2-(4-Chlorophenyl)benzo[b]thiophen-3(2H)-one 1,1dioxide (4c):  $C_{14}H_9ClO_3S$ , white solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.12 (dd, *J* = 15.8, 7.9 Hz, 2H), 8.03 (t, *J* = 7.7 Hz, 1H), 7.89 (t, *J* = 7.6 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.35 (dd, *J* = 6.6, 3.3 Hz, 2H), 5.18 (s, 1H). ESI-HRMS: calcd for  $C_{14}H_9ClNaO_3S^+([M + Na^+])$  314.9859, found 314.9862.

4-(1,1-Dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-2yl)benzonitrile (5c):  $C_{15}H_9NO_3S$ , white solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.16 (dd, *J* = 15.5, 7.8 Hz, 2H), 8.08 (t, *J* = 7.3 Hz, 1H), 7.94 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.43 (dd, *J* = 6.8, 3.2 Hz, 2H), 5.23 (s, 1H). ESI-HRMS: calcd for  $C_{15}H_9NNaO_3S^+([M + Na^+])$  306.0201, found 306.0197.

# 4. Conclusions

In summary, we have reported a new concise route to the synthesis of 2-arylbenzo[b]thiophen-3(2H)-one 1,1-dioxide via palladium-catalyzed  $C(sp^3)$ -H arylation of benzo[b] thiophen-3(2H)-one 1,1-dioxide (1a). Combined with the current research hotspot,  $C(sp^3)$ -H activation, this protocol can effectively save many steps and provide 1c and its derivatives in good to moderate yields.

# **Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

## **Conflicts of Interest**

The authors declare no conflicts of interest.

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