

# Mechanistic study of Pd/Ag-dual catalyzed cross dehydrogenative coupling of perfluoroarenes with thiophenes

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ABSTRACT: The mechanism of the Pd/Ag-dual-catalyzed cross dehydrogenative coupling (CDC) between perfluoroarenes and thiophenes was clarified. The exact role of the catalytic resting state of the homo biaryl-Pd(II) complex, which was previously overlooked in Pd/Ag-dual-catalyzed CDC, was carefully investigated. Detailed experimental studies indicated that a homo biaryl-Pd(II) complex occurred in the catalytic off-cycle as a resting state and prevented the homocoupling of perfluoroarenes. In addition, these studies indicated that the C-H bond activation steps of perfluoroarenes and thiophenes proceeded by different mechanisms. While the C-H bond

of perfluoroarenes was immediately activated by Ag(I) salts, the C-H bond of thiophenes was activated by the Pd(II) catalyst. Kinetic studies revealed that the Pd(II)-C-H activation of thiophenes is most likely the rate determining step.

## INTRODUCTION

The cross dehydrogenative coupling (CDC) reaction is a cross coupling reaction based on two heterolytic C-H bond cleavage steps. Due to its usefulness, this reaction has attracted much attention in the last 10 years.<sup>1-4</sup> However, during CDC, it is often difficult to completely control the order of the C-H activation steps of the two substrates. For this reason, undesired side-reactions, especially homocoupling reactions, may occur. Recently, CDC reactions showing high selectivity have been reported.<sup>5-11</sup> In particular, Ag salts have often been used as additives to improve the cross-coupling efficiency in homogeneous palladium catalysis.

The investigation of the multiple roles of Ag salts in C-H activation reactions has attracted considerable attention in the past decades.<sup>8,10-20</sup> In particular, direct arylation and oxidative coupling reactions using Au/Ag or Pd/Ag dual catalytic systems have been extensively studied. Although the use of Pd/Ag systems to perform C-H functionalization reactions is more common than that of Au/Ag systems, the latter were the first to be investigated from a mechanistic standpoint.

The promotion of Au-mediated C-H activation by Ag salts was first reported by the Larrosa group.<sup>12</sup> Later, the Nolan group suggested that in the case of such C-H activation reaction, the Ag salts activated the C-H bond, thus inducing the subsequent transmetalation with the Au complex.<sup>13</sup> More recently, the Zhu group reported detailed mechanistic and theoretical studies of Au/Ag-dual-catalyzed CDC.<sup>11</sup> The authors clarified that the Ag salts were the actual species involved in the C-

H bond activation of electron-deficient arenes via a concerted metalation-deprotonation (CMD) pathway.

Mechanistic studies of Pd/Ag-dual-catalyzed C-H activation reactions were also performed.<sup>8,15,16</sup> Furthermore, the role of Ag salts in Pd/Ag-dual-catalyzed C-H activation reactions was investigated independently by the Mori<sup>17</sup> and Sanford<sup>18</sup> groups. Reports by the Larrosa<sup>19,20</sup> and Hartwig<sup>21</sup> groups demonstrated that Ag salts played the role of oxidants and halide scavengers in the C-H activation of arenes upon direct arylation. Although the role of Ag salts has been actively studied in Pd/Ag-dual-catalyzed C-H activation reactions, the detailed reaction mechanism of Pd/Ag-dual-catalyzed CDC remains unclear. Especially, the key intermediates responsible for the high cross-coupling selectivity as well as the exact role of the Ag salts have not been elucidated.

In order to expand the application of CDC to materials science, it is important to identify the key intermediates, actual role of Ag salts, and mechanism of the Pd/Ag-dual-catalyzed CDC. In particular, details about the C-H bond cleavage steps and intermediates formed are useful for the reaction development.

Recently, our group described a highly selective Pd/Ag-dual-catalyzed CDC reaction and achieved the cross coupling polycondensation of perfluoroarenes with bithiophenes.<sup>22</sup> Almost no undesired homocoupling side product formation was observed. Therefore, we adopted this reaction system as a model and performed further studies to elucidate the mechanism of Pd/Ag-dual-catalyzed CDC as well as the role of Ag salts.

In this study, we reported the experimental mechanistic analysis of the Pd/Ag-dual-catalyzed CDC of perfluoroarenes with thiophenes, which includes a new proposition for a catalytic off-cycle. We revealed that the catalytic resting state—homo biaryl-Pd(II) complex Pd-(Ar<sup>pf</sup>)<sub>2</sub> [Ar<sup>pf</sup> = perfluoroarene], which has been overlooked previously—occurs in the catalytic off-cycle.

Moreover, we established that such resting state species is a key intermediate that causes for high cross-coupling selectivity. Moreover, our studies indicated that Ag(I) was the actual species responsible for the activation of the C-H bond of electron-deficient perfluoroarenes to form a perfluoroaryl-Ag(I) complex. The described Pd/Ag-dual-catalyzed mechanism includes the Ag(I)-mediated C-H activation of electron-deficient perfluoroarenes and Pd(II)-mediated C-H activation of thiophenes.

This system allows for a highly selective and efficient cross coupling of perfluoroarenes with thiophenes starting from two aromatic C-H bonds. Such selectivity originates from two different C-H activation steps as well as the presence of catalytic resting states. While Ag(I) favors the C-H activation of an electron-deficient perfluoroarene, Pd(II) activates the C-H bond of an electron-rich thiophene. Moreover, stable homo-biaryl Pd(II) complexes Pd-(Ar<sup>pf</sup>)<sub>2</sub>, which represent catalytic resting states, prevent the homocoupling of perfluoroarenes.

## RESULTS AND DISCUSSION

- Estimated mechanism

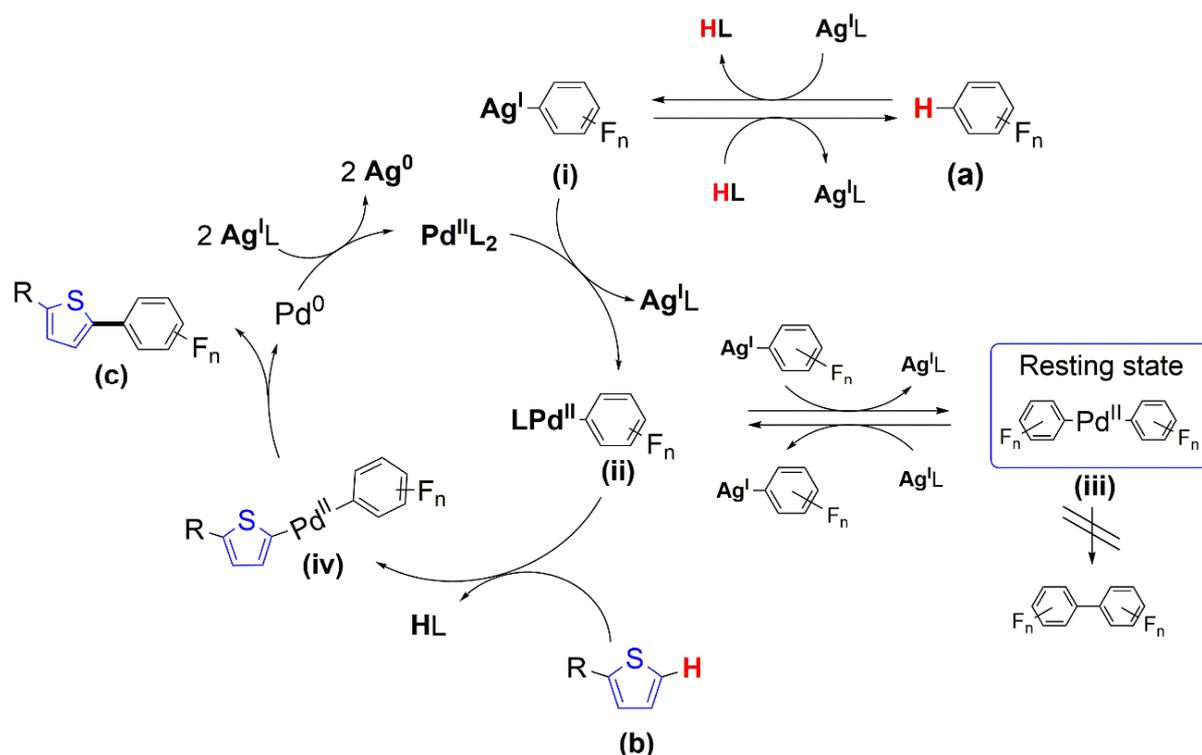


Figure 1. Estimated mechanism of Pd/Ag-dual catalyzed CDC of perfluoroarenes with thiophenes.

First, we assessed the mechanism of the Pd/Ag-dual-catalyzed CDC of perfluoroarenes with thiophenes as well as the role of Ag salts described in previous reports (Figure 1).<sup>8,15,16,18,19,22,23</sup> Such mechanism entails as first step the Ag(I)-mediated C-H activation of perfluoroarenes (a), which leads to the generation of Ag intermediate (i). In the second step, (i) reacts with a Pd catalyst and is converted to mono-aryl Pd(II) intermediate (ii). Next, thiophene (b) reacts with (ii) to afford hetero-biaryl Pd(II) intermediate (iv). Finally, the cross-coupling product (c) is produced by reductive elimination from (iv). The Pd catalyst is reoxidated by an oxidant and the catalytic cycle is thus completed. A homo-biaryl Pd(II) complex occurs in the catalytic off-cycle as the catalytic resting state.

We mostly focused on the following three points and hypothesized the requirements necessary for achieving a selective cross coupling reaction.

(1) The C-H bond activation step of perfluoroarenes

In CDC, it is assumed that the two substrates competitively react with the Pd catalyst. Based on previous findings, it was hypothesized that perfluoroarenes might preferentially react with the Pd catalyst. In order to achieve this, it is necessary to satisfy the following two requirements. Firstly, the C-H bond cleavage of perfluoroarenes (a) should immediately occur and form the Ag intermediate (i). Secondly, the transmetalation of the Pd catalyst with intermediate (i) also have to immediately occur to afford mono-aryl Pd intermediate (ii).

(2) Reactivity of the homo-biaryl Pd(II) complex

It is known that the homocoupling of perfluoroarenes hardly occurs. Therefore, we hypothesized that the reductive elimination from homo-biaryl Pd(II) complexes of type Pd-(Ar<sup>PF</sup>)<sub>2</sub> (iii) does not take place. In addition, we estimated that complex (iii) is in equilibrium with the catalytic active species (ii).

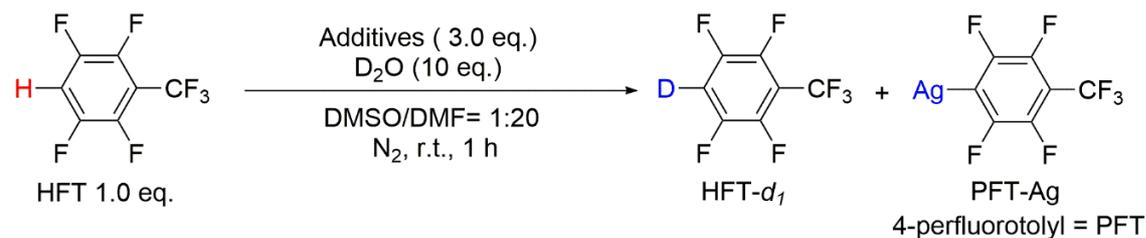
(3) The details of the C-H activation step and homocoupling pathway of thiophenes

It has been previously described that the Ag salts can also cleave the C-H bonds of electron-rich thiophenes.<sup>17,18,20,24</sup> On the other hand, it has been suggested that the Pd catalyst can also cleave the C-H bond of thiophenes.<sup>25,26</sup> Therefore, a possible C-H bond cleavage step and cross-coupling pathway of thiophenes (b) was investigated.

CDC reactions between electron-deficient perfluoroarenes and electron-rich thiophenes exhibited excellent selectivity without the need of adding a large excess of one of the substrates.<sup>7,8,14,22</sup> Nonetheless, only few experimental studies were conducted on the mechanism of Pd/Ag-dual-catalyzed CDC.<sup>8,16</sup> Therefore, in order to elucidate such mechanism, we performed the following studies with regard to the C-H bond activation of perfluoroarenes and thiophenes and the role of Ag salts.

· Deuterium substitution reaction of  $\alpha,\alpha,\alpha,2,3,5,6$ -heptafluorotoluene (HFT) of the model perfluoroarene

Table 1. H/D exchange experiments of HFT with D<sub>2</sub>O



Entry	Additives	HFT- <i>d</i> <sub>1</sub> (%)	PFT-Ag (%)
1	None	-	-
2	Ag <sub>2</sub> CO <sub>3</sub>	37	-
3	Ag <sub>2</sub> CO <sub>3</sub> , PivOH	24	-
4	AgOPiv	20	20
5	KOPiv	73	-
6	K <sub>2</sub> CO <sub>3</sub>	85	-
7	AgOPiv, K <sub>2</sub> CO <sub>3</sub>	4.6	92

Conditions: HFT 0.25 mmol (33.9  $\mu$ L, 1.0 eq.), additives 0.75 mmol (3.0 eq.), D<sub>2</sub>O 2.5 mmol (45.2  $\mu$ L, 10 eq.), DMSO/ DMF = 0.10 mL/2.0 mL, room temperature: used water bath 25 °C.

In order to determine the role of the Ag salts in the C-H bond activation step of perfluoroarenes, we performed H/D exchange experiments using HFT as model substrate and D<sub>2</sub>O (10 equiv. vs HFT) (Table 1). Experiments were conducted by referencing to previous studies.<sup>11,14,18</sup>

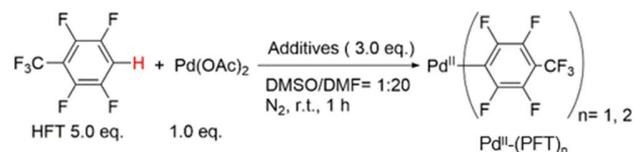
HFT-*d*<sub>1</sub> and PFT-Ag were detected in the <sup>19</sup>F NMR spectra run in DMSO-*d*<sub>6</sub>. It was found that in the presence of Ag salts and/or base, both deuteration and metalation of HFT occurred (entries 2-7). Especially, in the presence of AgOPiv, the intermediate PFT-Ag was observed by <sup>19</sup>F NMR

analysis despite the presence of 10 equivalents of D<sub>2</sub>O (entries 4, 7). The effectiveness of AgOPiv in the C-H bond activation is in agreement with previous findings.<sup>11,14,18</sup> In addition, when AgOPiv and K<sub>2</sub>CO<sub>3</sub> were added, PFT-Ag was mainly obtained (entry 7). These results suggested that PFT-Ag is stable under the employed conditions. Furthermore, it was established for the first time that a base was involved in promoting the Ag(I)-C-H bond activation. The <sup>19</sup>F NMR spectrum of a representative experiment (entry 7) is shown in Figure S1. The <sup>19</sup>F NMR spectrum and ORTEP drawing of isolated PFT-Ag are shown in Figure S9 and 10.

· Sub-stoichiometric investigation of transmetalation step<sup>18</sup>

Next, we performed the reaction of HFT with Pd(OAc)<sub>2</sub> in the presence of Ag salts and/or base to elucidate the transmetalation step of perfluoroarenes (Table 2).

Table 2. Effect of additives on the reaction of HFT with Pd(OAc)<sub>2</sub>



Entry	Additives	Conversion of Pd(OAc) <sub>2</sub> (%)
1	None	No reaction
2	Ag <sub>2</sub> CO <sub>3</sub>	No reaction
3	Ag <sub>2</sub> O	trace
4	AgOPiv	73
5	AgNO <sub>3</sub>	No reaction
6	K <sub>2</sub> CO <sub>3</sub>	No reaction
7	AgOPiv K <sub>2</sub> CO <sub>3</sub>	93

Conditions: HFT(a) 0.25 mmol (5.0 eq.), Pd(OAc)<sub>2</sub> 0.050 mmol (1.0 eq.), DMSO/DMF = 0.10 mL/ 2.0 mL, additives 0.75 mmol, room temperature: used water bath 25 °C.

The reactions were followed by <sup>19</sup>F NMR spectroscopy. In the presence of only AgOPiv, the palladation of HFT occurred (entry 4). Figure 2 shows the corresponding <sup>19</sup>F NMR spectrum. It was assumed that the Pd complex formed in this reaction was a Pd-(PFT)<sub>2</sub> species in which two PFT were coordinated to a Pd catalyst.<sup>18</sup> A minor peak was observed around -110 ppm, which is believed to be due to complexes to which different ligands are coordinated or structural isometric complexes.

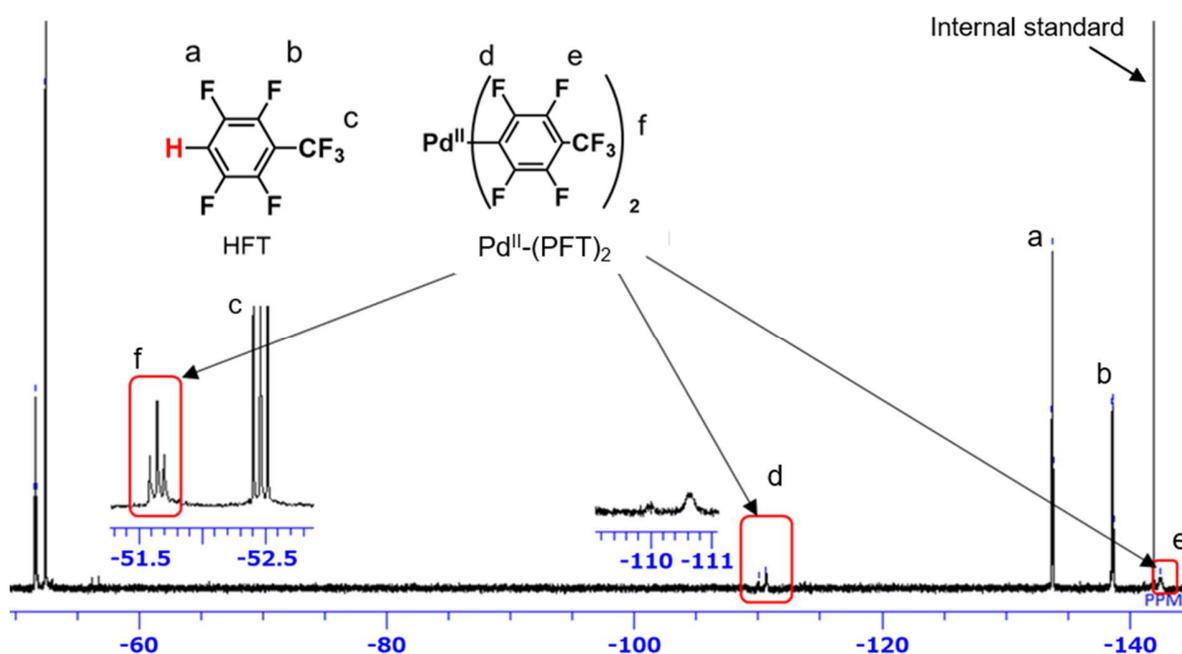


Figure 2. <sup>19</sup>F NMR spectrum of palladation of HFT: Entry 4 (DMSO- *d*<sub>6</sub>, 376.5 MHz).

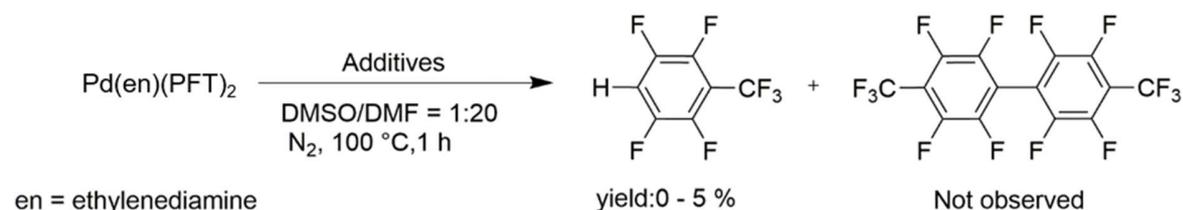
In contrast, even in the presence of other Ag salts (Ag<sub>2</sub>CO<sub>3</sub>, Ag<sub>2</sub>O, and AgNO<sub>3</sub>), the reaction did not occur (entries 2, 3, and 5). These results suggested that the Ag(I)-C-H activation proceeds via

a CMD pathway as previously reported.<sup>18</sup> Moreover, K<sub>2</sub>CO<sub>3</sub> did not contribute to the palladation despite promoting the deuteration of HFT (entry 6). However, when K<sub>2</sub>CO<sub>3</sub> was added together with AgOPiv, Pd-(PFT)<sub>2</sub> was obtained in 93% yield (entry 7). These results indicated that the intermediate PFT-Ag plays an important role in order for the palladation reaction to proceed. In brief, it was suggested that the reaction proceeds via transmetalation of PFT-Ag with a Pd catalyst.

Even when the reaction mixture containing Pd-(PFT)<sub>2</sub> was heated at 100 °C for 1 h, no homocoupling product was observed by <sup>19</sup>F NMR. This result indicated that Pd-(PFT)<sub>2</sub> is relatively stable. Next, we attempted to investigate the reactivity of a homo-biaryl Pd(II) complex using a model complex.

To this end, we carried out stoichiometric experiments using Pd(en)(PFT)<sub>2</sub> as the model Pd(II) complex and PivOH and AgOPiv (Table 3) as the main additives<sup>18, 27</sup>. The ORTEP drawing and <sup>19</sup>F NMR spectrum of Pd(en)(PFT)<sub>2</sub> are shown in Figure S11 and 12.

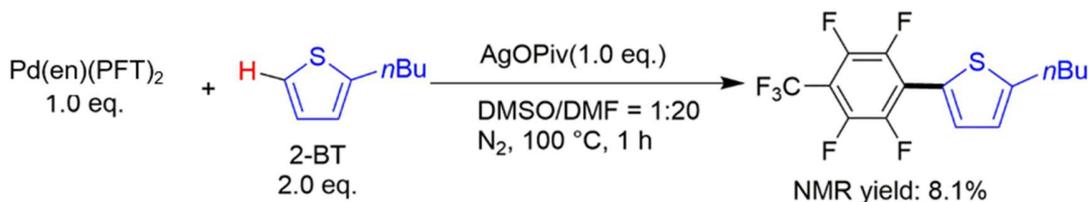
Table 3. Investigation of the reactivity of homo-biaryl Pd(II) complex



Entry	Additives (1.0 eq.)	Yield of HFT(%) <sup>a</sup>
1	None	<trace
2	PivOH	<trace
3	AgOPiv	5

Conditions: Pd(en)(PFT)<sub>2</sub> 0.010 mmol (1.0 eq.), additives: 0.010 mmol (1.0 eq.), DMSO/DMF = 25 μL/500 μL, a: the conversion was estimated by yield of HFT and PFT-Ag calculated using <sup>19</sup>F NMR.

When Pd(en)(PFT)<sub>2</sub> was reacted with PivOH (1.0 eq.) at 100 °C for 1 h, the reaction did not proceed and all raw materials were recovered (entry 2). On the other hand, in the presence of AgOPiv (1.0 eq.), 5% HFT and mono-aryl Pd(II) complex were observed by <sup>19</sup>F NMR (entry 3). This result suggested that the active species were generated by a ligand exchange reaction between homo-biaryl Pd(II) and Ag salts. The yield of HFT was as low as 5% for this experiment. This may be due to the structure and stability of Pd(en)(PFT)<sub>2</sub>. Because Pd(en)(PFT)<sub>2</sub> has a bidentate ligand, ethylenediamine, which rigidly binds to a Pd (II) center, the ligand exchange reaction barely proceeded.

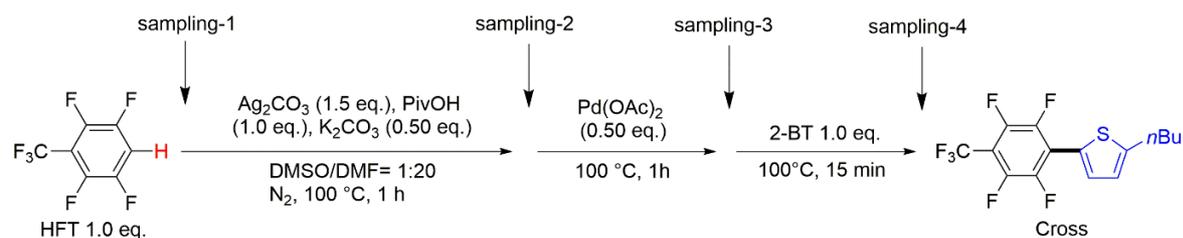


Scheme 1. The stoichiometric coupling experiment of Pd(en)(PFT)<sub>2</sub> with 2-BT.

We next carried out a stoichiometric reaction with Pd(en)(PFT)<sub>2</sub> and 2-BT in the presence of AgOPiv (1.0 eq.) at 100 °C for 1 h (Scheme 1). The yield of the cross-coupling product was calculated based on the <sup>19</sup>F NMR results (Figure S3) and found to be 8.1%. As shown in Table 3, the low yield results because the ligand exchange reaction of Pd(en)(PFT)<sub>2</sub> was difficult. This finding supports the assumption that the homo-biaryl Pd(II) complex Pd-(Ar<sup>Pf</sup>)<sub>2</sub> is not a catalytic deactivated species, while the monoaryl Pd(II) complex formed during the reaction is the catalytically active species. In all experiments presented in Table 3 and Scheme 1, no homocoupling product was observed. These studies using model complexes support the hypothesis that a homo-biaryl Pd(II) complex Pd-(Ar<sup>Pf</sup>)<sub>2</sub> is the catalytic resting state and has an important role to prevent the homocoupling of perfluoroarenes.

· Reactivity investigation of *in situ* generated intermediates by following stepwise cross coupling reaction

Table 4. Stepwise cross dehydrogenative coupling experiments with HFT and 2-BT



Sampling	HFT (%)	PFT-Ag (%)	Pd complexes <sup>※</sup> (%)	Cross (%)
1	100	-	-	-
2	26	74	-	-
3	-	-	~100	-
4	-	-	34	66

The condition is based on the previous report.<sup>22</sup>

<sup>※</sup> Pd complexes: homo-biaryl Pd(II) complex (Pd-(PFT)<sub>2</sub>) and monoaryl Pd(II) complex (Pd-(PFT))

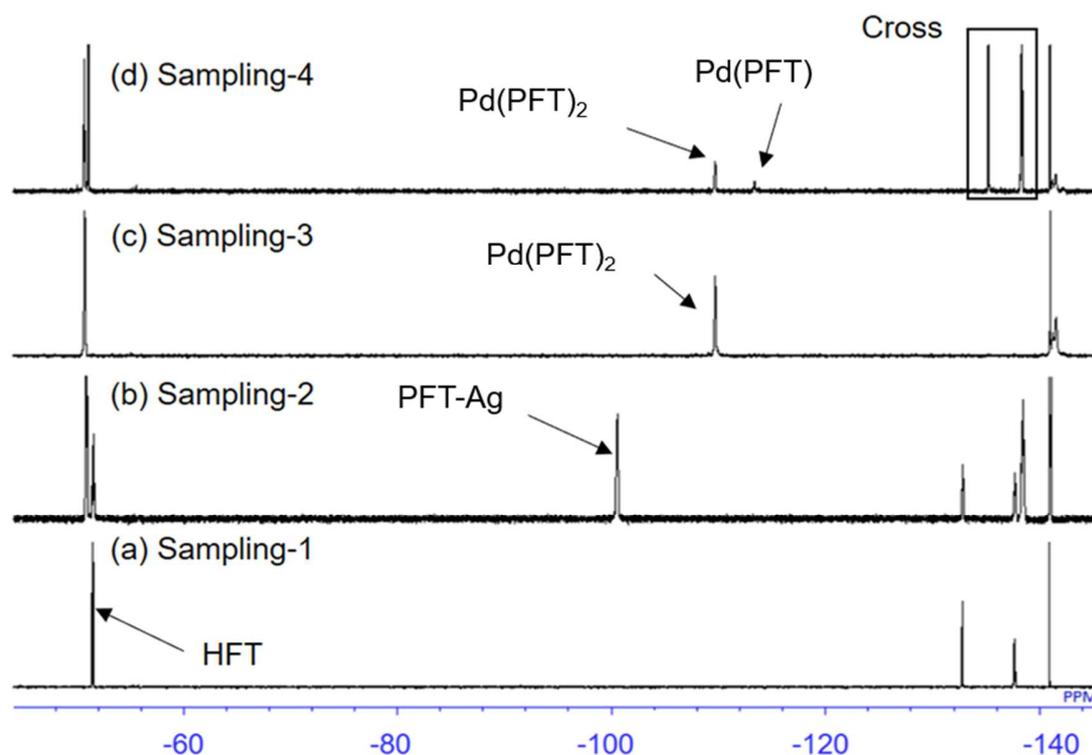


Figure 3.  $^{19}\text{F}$  NMR spectra of stepwise CDC experiments (DMSO-  $d_6$ , 376.5 MHz): (a) reference spectrum, (b) after HFT reacted with Ag salts, (c) after added  $\text{Pd}(\text{OAc})_2$ , (d) after added 2-BT.

Few studies were reported describing the direct tracing of the CDC reaction process (*in situ* formation of intermediates, transmetalation, and coupling reaction) by NMR spectroscopy.<sup>11,18</sup> We performed a stepwise model CDC and traced the elementary step in the process using  $^{19}\text{F}$  NMR (Table 4). The tracing was carried out before the reaction (sampling-1), after adding the Ag salts (sampling-2), after adding  $\text{Pd}(\text{OAc})_2$  (sampling-3), and after adding 2-BT (sampling-4). The  $^{19}\text{F}$  NMR spectra measured for each process are shown in Figure 3.

When HFT, Ag salts, and additives were reacted at 100 °C for 1 h, PFT-Ag (spectrum peak: about -100 ppm) was formed (sampling-2, Figure 3-b). This result revealed that PFT-Ag stably exists under the reaction conditions. Subsequently, after 0.5 equivalents of  $\text{Pd}(\text{OAc})_2$  was added

and the reaction was continued for 1 h, both HFT and PFT-Ag were converted to Pd-(PFT)<sub>2</sub> (spectral peak: about -110 ppm) (sampling-3, Figure 3-c). Since the spectral peak at about -113 ppm corresponding to the monoaryl Pd(II) complex coordinated with one HFT at the Pd was not observed, it was concluded that Pd-(PFT)<sub>2</sub> was more stable than a mono-aryl Pd(II) complex. In addition, these results supported the transmetalation of HFT with the Pd catalyst via PFT-Ag. Finally, after addition of 1.0 equivalents of 2-BT and heating at 100 °C for 15 min, a cross coupling product was observed with an NMR yield of 66% (sampling-4, Figure 3-d). It is assumed that the peak occurring in the vicinity of -113 ppm derives from a monoaryl Pd(II) complex.<sup>18</sup> This result confirmed the observation that Pd-(PFT)<sub>2</sub> is not a catalytically inactive species.

The results illustrated in Table 4 and Figure 3 are consistent with our results derived from the mechanistic studies. In addition, these experiments aided to elucidate the reactivity and role of PFT-Ag and Pd-(PFT)<sub>2</sub>, as discussed below.

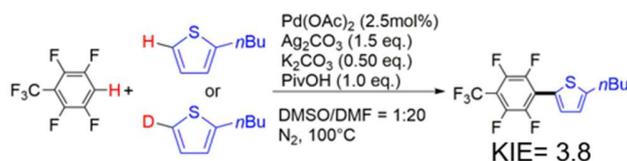
- PFT-Ag is a relatively stable complex and an important intermediate in the CDC reaction. The transmetalation of PFT-Ag with the Pd catalyst easily and rapidly proceeds in the system.
- Pd-(PFT)<sub>2</sub> does not directly participate to the reaction, however it is a catalytically resting state since it is in equilibrium with the catalytic active species.

#### Kinetic analysis

A kinetic analysis of the CDC reaction under standard conditions was performed.

- Investigation of rate determining step: kinetic isotope effect studies<sup>8,11</sup>

In order to investigate the rate determining step of the CDC between perfluoroarenes and thiophenes, kinetic isotope effect (KIE) experiments were performed.<sup>28</sup>



Scheme 2. KIE experiments: the reaction of HFT with 2-BT or 2-BT-*d*<sub>1</sub>.

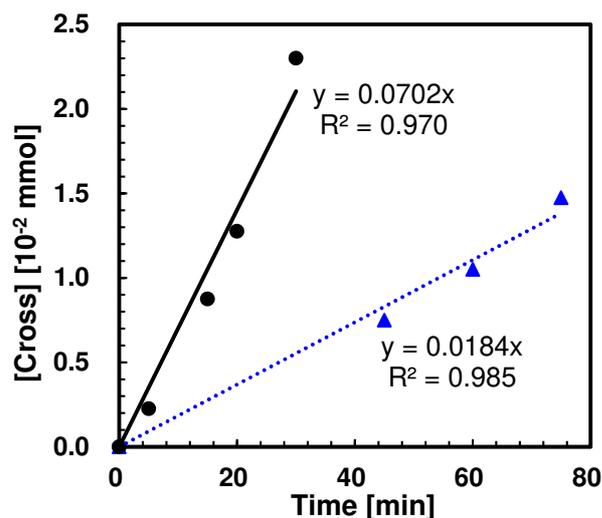
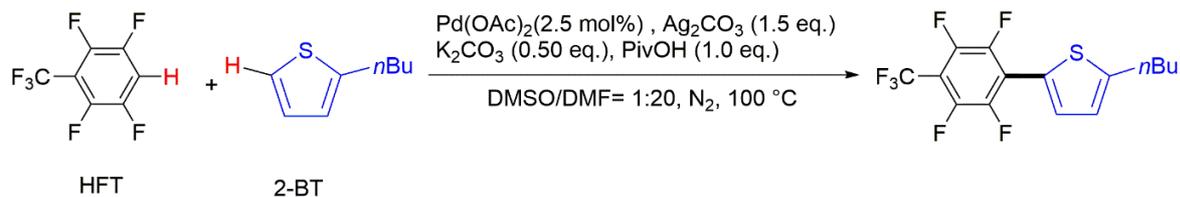


Figure 4. the results of KIE experiments (black cycles and the solid line: the reaction of HFT with 2-BT, blue triangles and the dash line: the reaction of HFT with 2-BT-*d*<sub>1</sub>).

The measurement of the KIE was carried out using HFT and 2-BT under standard conditions (Scheme 2).<sup>22</sup> As a result, the  $k_H/k_D$  was found to be 3.8 (Figure 4), suggesting that the C-H cleavage step of 2-BT was the rate determining step in the catalytic process. This result is consistent with the results of similar reactions previously reported.<sup>8</sup>

· Investigation of kinetic order measurements<sup>29–32</sup>

In order to obtain further insight into the C-H activation step of thiophenes, kinetic order measurements were performed under standard conditions. The initial reaction rate was the rate up to the time when the yield of the cross-coupling product was 10% or less. These conditions were similar to those used in a previous study.<sup>22</sup>



Standard conditions: HFT 0.25 mmol (33.9  $\mu\text{L}$ , 1.0 eq.), 2-BT 0.25 mmol (36.8  $\mu\text{L}$ , 1.0 eq.), DMSO/DMF= 1/20 (0.10 mL/2.0 mL), Pd(OAc)<sub>2</sub> 0.0063 mmol (1.41 mg, 2.5 mol%), Ag<sub>2</sub>CO<sub>3</sub> 0.38 mmol (103 mg, 1.5 eq.), K<sub>2</sub>CO<sub>3</sub> 0.13 mmol (17.3 mg, 0.50 eq.), PivOH 0.25 mmol (28.2  $\mu\text{L}$ , 1.0 eq.), under N<sub>2</sub>, 100 °C

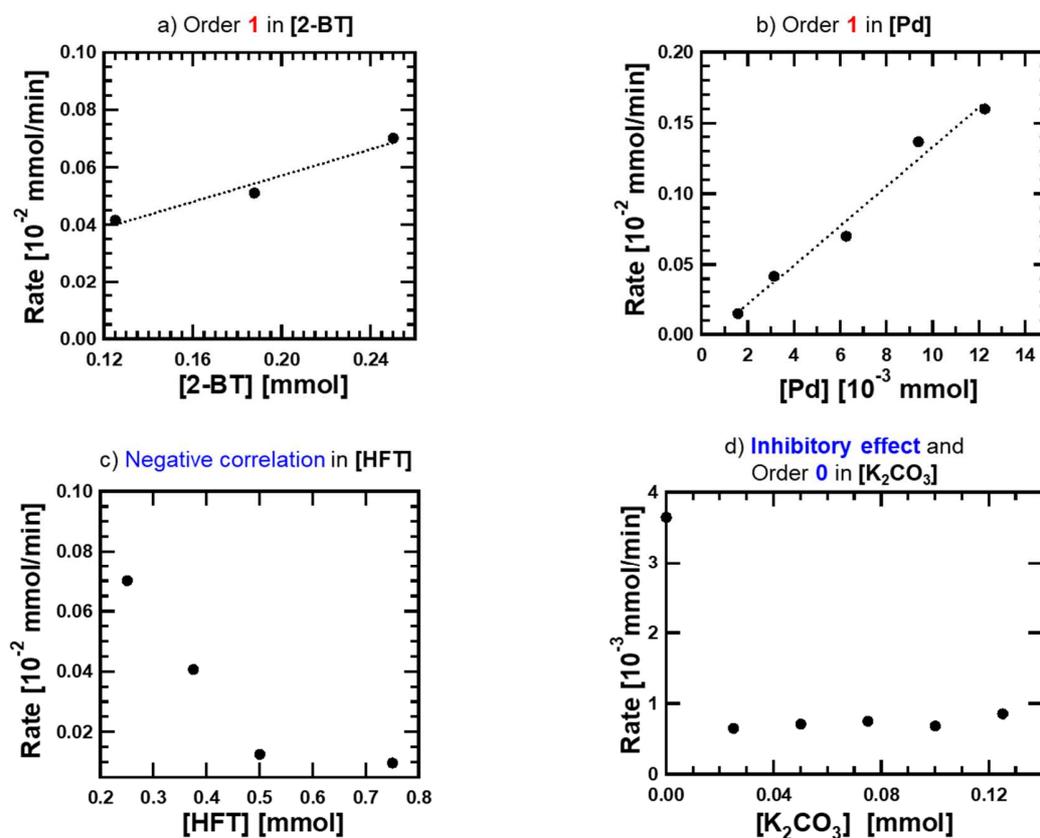


Figure 5. Kinetic order measurements: determination of the order in (a) 2-BT, (b) Pd catalyst, (c) HFT, (d) K<sub>2</sub>CO<sub>3</sub>. The results of a) and b) were similar to the findings of the previous research.<sup>11</sup>

As shown in Figure 5, a first order dependence on [2-BT] and [Pd] was observed. These results indicate that 2-butylthiophene and palladium(II) are involved in the rate-determining step. Namely, these results are consistent with the results of the KIE experiments (Scheme 2) in which C-H

activation of 2-BT is the rate-determining step. In addition, the C-H activation was likely caused by the Pd catalyst because first-order dependence on [Pd] was observed.

In contrast, it was interesting to note a negative order dependence on [HFT]. Furthermore, an inhibition effect and zero order dependence on [K<sub>2</sub>CO<sub>3</sub>] was also observed. These results were not reported earlier and represented an unusual kinetic phenomenon. Since the addition of HFT and K<sub>2</sub>CO<sub>3</sub> promotes the formation of a homo-biaryl Pd(II) complex, it can be suggested that the amount of active species as well as the reaction rate decreased. Therefore, these specific results supported the existence of catalytic resting states. The kinetic results for each factor showed that the Pd(II)-C-H activation of 2-BT was actually the rate determining step in the Pd/Ag-dual-catalyzed CDC. Moreover, the unusual rate dependence on [HFT] and [K<sub>2</sub>CO<sub>3</sub>] supports the presence of a catalytic resting state, namely Pd-(PFT)<sub>2</sub>, in the off-cycle. By taking these mechanistic studies into consideration, a plausible mechanism for the Pd/Ag-dual-catalyzed dehydrogenative coupling of HFT with 2-BT is proposed in Figure S8.

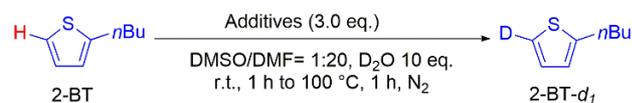
#### Investigation of cause of homo-coupling reaction of thiophenes

Next, we focused on the undesired homocoupling of thiophenes during the reaction. In order to gain further insight into the C-H cleavage step of thiophenes and investigate the homocoupling pathway, deuteration experiments and oxidative homocoupling reactions were carried out.

- Deuterium substitution reaction of model compound 2-BT<sup>8,11,14,17,18,20</sup>

H/D exchange experiments using 2-BT and D<sub>2</sub>O (10 equivalents to 2-BT) were carried out in the presence of various additives (Table 5).

Table 5. H/D exchange experiments of 2-BT with D<sub>2</sub>O



Entry	Additives	2-BT- <i>d</i> <sub>1</sub> (%)	
		r.t. 1 h	100 °C 1 h
1	None	No reaction	No reaction
2	Ag <sub>2</sub> CO <sub>3</sub>	No reaction	4.2
3	Ag <sub>2</sub> CO <sub>3</sub> , PivOH	No reaction	37
4	AgOPiv	No reaction	43
5	K <sub>2</sub> CO <sub>3</sub>	No reaction	No reaction
6	AgOPiv, K <sub>2</sub> CO <sub>3</sub>	No reaction	67

Conditions: 2-BT 0.25 mmol (36.8 μL, 1.0 eq.), additives 0.75 mmol, D<sub>2</sub>O 2.5 mmol (45.2 μL, 10 eq.), DMSO/DMF=0.10 mL/2.0 mL.

The deuteration ratio was calculated by observing the disappearance of the proton at the  $\alpha$ -position of 2-BT by <sup>1</sup>H NMR spectroscopy. A typical example is shown in Figure S2.

Unlike the case of HFT, the deuteration reaction of 2-BT did not proceed at room temperature in all cases (entries 1-6), most likely because the acidity of the C-H bond at the  $\alpha$ -position of 2-BT is low. However, upon heating at 100 °C for 1 h, the deuteration reaction proceeded only in the presence of Ag salts (entries 2, 3, 4, and 6). In particular, AgOPiv was found to be effective in the deuteration reaction of 2-BT. In addition, although K<sub>2</sub>CO<sub>3</sub> alone did not contribute to the deuteration reaction, it was shown that adding K<sub>2</sub>CO<sub>3</sub> together with AgOPiv has a synergistic effect on the deuteration reaction (entry 6).

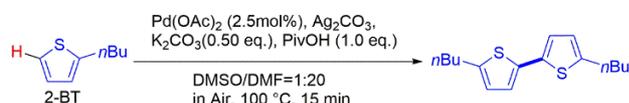
These results indicated that the Ag salts, particularly AgOPiv, was effective for activating the C-H bond at the  $\alpha$ -position of 2-BT. Similar results have been obtained in previous studies.<sup>14,18</sup>

Although the base could not activate the C-H bond of 2-BT under the reaction conditions, it was evident that the concomitant presence with the Ag salts did promote the deuteration reaction. This is probably due to the fact that the base may promote the transmetalation of 2-BT with the Ag salts.

·Oxidative homo-coupling reaction of 2-BT<sup>17,18</sup>

It is known that Ag salts promote the oxidative homocoupling reaction of thiophenes. However, the direct examination of the relationship between the homocoupling reaction of thiophenes generated under the CDC reaction conditions and the addition of Ag salts or their quantitative dependence was not reported to date. In order to investigate the effect of the Ag salts on the oxidative homocoupling reaction, the reaction of 2-BT was carried out in the presence of various amounts of Ag salts (Table 6). The yields of the homocoupling product were calculated from the corresponding <sup>1</sup>H NMR spectrum (Figure S13).

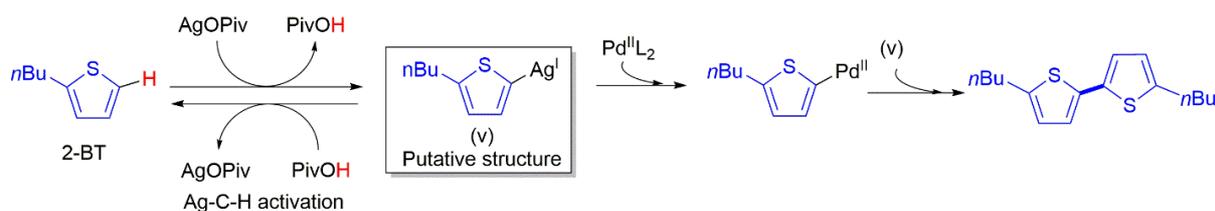
Table 6. Oxidative homo-coupling of 2-BT with various amounts of Ag salts



Entry	Ag <sub>2</sub> CO <sub>3</sub> (mol%)	Homo (%)
1	150	14.7
2	100	14.3
3	50	12.8
4	30	9.7
5	10	< 5

It was found that the higher was the amount of Ag salt added, the higher was the yield of homo-coupled product, and the more effective was the oxidative homocoupling reaction (entries 1-5). In addition, the reaction of 1 equivalent of Pd without adding Ag salt did not efficiently proceed

(Table S5, entry 2), and the reaction did not proceed without Pd(OAc)<sub>2</sub> (Table S5, entry 3). These results suggested that the Ag salts cleaved the C-H bond of 2-BT during the reaction. Therefore, the addition of a large excess of Ag salts may induce the homocoupling reaction. Based on these results as well as previous reports,<sup>17,18,20,24</sup> a potential pathway for the oxidative homocoupling reaction of 2-BT is shown in Scheme 3.



Scheme 3. The putative reaction pathway of oxidative homo-coupling.

These results suggest that the oxidative homocoupling reaction proceeds following a similar pathway to that of the CDC reaction. In addition, the Ag salts promote the oxidative homocoupling of thiophenes. Therefore, the excess amount of Ag salts may induce the homocoupling of thiophenes during the Pd/Ag-dual-catalyzed CDC. The intermediate 2-BT-Ag was unstable and could not be detected by <sup>1</sup>H NMR as previously reported.<sup>18</sup> Since the bis-thienyl Pd(II) complex Pd-(2-BT)<sub>2</sub> cannot be detected by <sup>1</sup>H NMR, it was concluded that Pd-(2-BT)<sub>2</sub> was the unstable intermediate.<sup>17</sup> Hence, it was considered that the reductive elimination from Pd-(2-BT)<sub>2</sub> easily occurred and the homocoupling reaction of 2-BT thus proceeded.

## CONCLUSION

In this study, we have clarified the mechanism of the Pd/Ag-dual-catalyzed cross dehydrogenative coupling of perfluoroarenes with thiophenes. Notably, a detailed mechanistic study revealed that a homo biaryl-Pd(II) complex such as Pd-(Ar<sup>pf</sup>)<sub>2</sub> occurred in the catalytic off-cycle serving as a catalytic resting state. Furthermore, we established that Pd-(Ar<sup>pf</sup>)<sub>2</sub> played an important role in preventing the homocoupling of perfluoroarenes. In addition, it was revealed that Ag(I) immediately activates the C-H bond of perfluoroarenes, while Pd(II) activates the C-H bond of thiophenes. It was suggested that the excess amount of Ag salts induced the oxidative homocoupling of thiophenes based on the investigation of their homocoupling pathway. This study contributes to increasing the knowledge about the catalytic C-H bond activation reaction using Ag salts, while also providing useful information about the mechanism of the Pd/Ag-dual-catalyzed CDC reaction.

## ASSOCIATED CONTENT

### Supporting Information

Experimental sections and characterization data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Yuto Shimoyama; Designed and performed experiments, analyzed data and wrote the paper.

Junpei Kuwabara; collected the data of single crystal X-ray diffraction and Supervised the research.

Takaki Kanbara; Supervised the research.

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### **Notes**

The authors declare no competing financial interest.

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### **REFERENCES**

- (1) Stuart, D. R.; Fagnou, K. The Catalytic Cross-Coupling of Unactivated Arenes. *Science*. **2007**, *316*, 1172–1175. DOI: 10.1126/science.1141956.
- (2) Yang, Y.; Lan, J.; You, J. Oxidative C-H/C-H Coupling Reactions between Two (Hetero)Arenes. *Chem. Rev.* **2017**, *117*, 8787–8863. DOI: 10.1021/acs.chemrev.6b00567.
- (3) Simonetti, M.; Cannas, D. M.; Larrosa, I. Biaryl Synthesis via C-H Bond Activation: Strategies and Methods, 1st ed.; Elsevier Inc., **2017**; Vol. 67. DOI: 10.1016/bs.adomc.2017.03.002.
- (4) Funes-Ardoiz, I.; Maseras, F. Oxidative Coupling Mechanisms: Current State of Understanding. *ACS Catal.* **2018**, *8*, 1161–1172. DOI: 10.1021/acscatal.7b02974.
- (5) Hull, K. L.; Sanford, M. S. Catalytic and Highly Regioselective Cross-Coupling of Aromatic C-H Substrates. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905. DOI: 10.1021/ja074395z
- (6) Hull, K. L.; Sanford, M. S. Mechanism of Benzoquinone-Promoted Palladium-Catalyzed Oxidative Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 9651–9653. DOI: 10.1021/ja901952h
- (7) He, C. Y.; Fan, S.; Zhang, X. Pd-Catalyzed Oxidative Cross-Coupling of Perfluoroarenes with Aromatic Heterocycles. *J. Am. Chem. Soc.* **2010**, *132*, 12850–12852. DOI: 10.1021/ja106046p.
- (8) He, C. Y.; Min, Q. Q.; Zhang, X. Palladium-Catalyzed Aerobic Dehydrogenative Cross-Coupling of Polyfluoroarenes with Thiophenes: Facile Access to Polyfluoroarene-Thiophene Structure. *Organometallics* **2012**, *31*, 1335–1340. DOI: 10.1021/om200873j.

- (9) He, C. Y.; Wang, Z.; Wu, C. Z.; Qing, F. L.; Zhang, X. Pd-Catalyzed Oxidative Cross-Coupling between Two Electron Rich Heteroarenes. *Chem. Sci.* **2013**, *4*, 3508–3513. DOI: 10.1039/c3sc51278a.
- (10) Cambeiro, X. C.; Ahlsten, N.; Larrosa, I. Au-Catalyzed Cross-Coupling of Arenes via Double C-H Activation. *J. Am. Chem. Soc.* **2015**, *137*, 15636–15639. DOI: 10.1021/jacs.5b10593.
- (11) Li, W.; Yuan, D.; Wang, G.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Cooperative Au/Ag Dual-Catalyzed Cross-Dehydrogenative Biaryl Coupling: Reaction Development and Mechanistic Insight. *J. Am. Chem. Soc.* **2019**, *141*, 3187–3197. DOI: 10.1021/jacs.8b12929.
- (12) Lu, P.; Boorman, T. C.; Slawin, A. M. Z.; Larrosa, I. Gold(I)-Mediated C–H Activation of Arenes. *J. Am. Chem. Soc.* **2010**, *132*, 5580–5581. DOI: 10.1021/ja101525w
- (13) Patrick, S. R.; Boogaerts, I. I. F.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. The Role of Silver Additives in Gold-Mediated C-H Functionalisation. *Beilstein J Org Chem.* **2011**, *7*, 892–896. DOI: 10.3762/bjoc.7.102.
- (14) Kang, L. J.; Xing, L.; Luscombe, C. K. Exploration and Development of Gold- and Silver-Catalyzed Cross Dehydrogenative Coupling toward Donor-Acceptor  $\pi$ -Conjugated Polymer Synthesis. *Polym. Chem.* **2019**, *10*, 486–493. DOI: 10.1039/c8py01162a.
- (15) Tang, S. Y.; Yu, H. Z.; You, W. L.; Guo, Q. X. Mechanistic Study of Palladium-Catalyzed Oxidative C-H/C-H Coupling of Polyfluoroarenes with Simple Arenes. *Chinese J. Chem. Phys.* **2013**, *26*, 415–423. DOI: 10.1063/1674-0068/26/04/415-423.
- (16) Li, H.; Liu, J.; Sun, C. L.; Li, B. J.; Shi, Z. J. Palladium-Catalyzed Cross-Coupling of Polyfluoroarenes with Simple Arenes. *Org. Lett.* **2011**, *13*, 276–279. DOI: 10.1021/ol102688e.

(17) Sugie, A.; Furukawa, H.; Suzuki, Y.; Osakada, K.; Akita, M.; Monguchi, D.; Mori, A. Electrophilic Substitution of Thiophenes with Aryl Palladium (II) and Platinum (II) Complexes: Mechanistic Studies on Palladium-Catalyzed C-H Arylation of Thiophenes. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 555–562. DOI: 10.1246/bcsj.82.555

(18) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. Role of Silver Salts in Palladium-Catalyzed Arene and Heteroarene C-H Functionalization Reactions. *Organometallics* **2017**, *36*, 165–171. DOI: 10.1021/acs.organomet.6b00437.

(19) Whitaker, D.; Burés, J.; Larrosa, I. Ag(I)-Catalyzed C-H Activation: The Role of the Ag(I) Salt in Pd/Ag-Mediated C-H Arylation of Electron-Deficient Arenes. *J. Am. Chem. Soc.* **2016**, *138*, 8384–8387. DOI: 10.1021/jacs.6b04726.

(20) Colletto, C.; Panigrahi, A.; Fernández-Casado, J.; Larrosa, I. Ag(I)-C-H Activation Enables Near-Room-Temperature Direct  $\alpha$ -Arylation of Benzo[b]Thiophenes. *J. Am. Chem. Soc.* **2018**, *140*, 9638–9643. DOI: 10.1021/jacs.8b05361.

(21) Lee, S. Y.; Hartwig, J. F. Palladium-Catalyzed, Site-Selective Direct Allylation of Aryl C-H Bonds by Silver-Mediated C-H Activation: A Synthetic and Mechanistic Investigation. *J. Am. Chem. Soc.* **2016**, *138*, 15278–15284. DOI: 10.1021/jacs.6b10220.

(22) Aoki, H.; Saito, H.; Shimoyama, Y.; Kuwabara, J.; Yasuda, T.; Kanbara, T. Synthesis of Conjugated Polymers Containing Octafluorobiphenylene Unit via Pd-Catalyzed Cross-Dehydrogenative-Coupling Reaction. *ACS Macro Lett.* **2018**, *7*, 90–94. DOI: 10.1021/acsmacrolett.7b00887.

- (23) Bay, K. L.; Yang, Y. F.; Houk, K. N. Multiple Roles of Silver Salts in Palladium-Catalyzed C-H Activations. *J. Organomet. Chem.* **2018**, *864*, 19–25. DOI: 10.1016/j.jorganchem.2017.12.026.
- (24) Masui, K.; Ikegami, H.; Mori, A. Palladium-Catalyzed C-H Homocoupling of Thiophenes: Facile Construction of Bithiophene Structure. *J. Am. Chem. Soc.* **2004**, *126*, 5074–5075. DOI: 10.1021/ja031855p.
- (25) Kuwabara, J.; Sakai, M.; Zhang, Q.; Kanbara, T. Mechanistic Studies and Optimisation of a Pd-Catalysed Direct Arylation Reaction Using Phosphine-Free Systems. *Org. Chem. Front.* **2015**, *2*, 520–525. DOI: 10.1039/c4qo00351a.
- (26) Wang, L.; Carrow, B. P. Oligothiophene Synthesis by a General C–H Activation Mechanism: Electrophilic Concerted Metalation-Deprotonation (eCMD). *ACS Catal.* **2019**, *9*, 6821–6836. DOI: 10.1021/acscatal.9b01195.
- (27) Koizumi, T. A.; Yamazaki, A.; Yamamoto, T. Reductive Elimination of C<sub>6</sub>F<sub>5</sub>–C<sub>6</sub>F<sub>5</sub> in the Reaction of Bis(Pentafluorophenyl)Palladium(II) Complexes with Protic Acids. *J. Chem. Soc. Dalton Trans.* **2008**, *2*, 3949–3952. DOI: 10.1039/b802408a.
- (28) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chemie - Int. Ed.* **2012**, *51*, 3066–3072. DOI: 10.1002/anie.201107334.
- (29) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. Mechanistic Study of Alcohol Oxidation by the Pd(OAc)<sub>2</sub>/O<sub>2</sub>/DMSO Catalyst System and Implications for the Development of Improved Aerobic Oxidation Catalysts. *J. Am. Chem. Soc.* **2002**, *124*, 766–767. DOI: 10.1021/ja016806w.

(30) Diao, T.; Pun, D.; Stahl, S. S. Aerobic Dehydrogenation of Cyclohexanone to Cyclohexenone Catalyzed by Pd(DMSO)<sub>2</sub>(TFA)<sub>2</sub>: Evidence for Ligand-Controlled Chemoselectivity. *J. Am. Chem. Soc.* **2013**, *135*, 8205–8212. DOI: 10.1021/ja4031648.

(31) Wang, D.; Stahl, S. S. Pd-Catalyzed Aerobic Oxidative Biaryl Coupling: Non-Redox Cocatalysis by Cu(OTf)<sub>2</sub> and Discovery of Fe(OTf)<sub>3</sub> as a Highly Effective Cocatalyst. *J. Am. Chem. Soc.* **2017**, *139*, 5704–5707. DOI: 10.1021/jacs.7b01970.

(32) Wang, D.; Izawa, Y.; Stahl, S. S. Pd-Catalyzed Aerobic Oxidative Coupling of Arenes: Evidence for Transmetalation between Two Pd(II)-Aryl Intermediates. *J. Am. Chem. Soc.* **2014**, *136*, 9914–9917. DOI: 10.1021/ja505405u.