

Review

Palladium-Catalyzed Cross-Coupling Reactions of Perfluoro Organic Compounds

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Received: 25 June 2014; in revised form: 19 August 2014 / Accepted: 21 August 2014 /

Published: 10 September 2014

Abstract: In this review, we summarize our recent development of palladium(0)-catalyzed cross-coupling reactions of perfluoro organic compounds with organometallic reagents. The oxidative addition of a C–F bond of tetrafluoroethylene (TFE) to palladium(0) was promoted by the addition of lithium iodide, affording a trifluorovinyl palladium(II) iodide. Based on this finding, the first palladium-catalyzed cross-coupling reaction of TFE with diarylzinc was developed in the presence of lithium iodide, affording α,β,β -trifluorostyrene derivatives in excellent yield. This coupling reaction was expanded to the novel Pd(0)/PR₃-catalyzed cross-coupling reaction of TFE with arylboronates. In this reaction, the trifluorovinyl palladium(II) fluoride was a key reaction intermediate that required neither an extraneous base to enhance the reactivity of organoboronates nor a Lewis acid additive to promote the oxidative addition of a C–F bond. In addition, our strategy utilizing the synergetic effect of Pd(0) and lithium iodide could be applied to the C–F bond cleavage of unreactive hexafluorobenzene (C₆F₆), leading to the first Pd(0)-catalyzed cross-coupling reaction of C₆F₆ with diarylzinc compounds.

Keywords: C–F bond activation; palladium; perfluoroalkene; perfluoroarene; cross-coupling; diarylzinc; arylboronate

1. Introduction

Efficient methods have been developed for the synthesis of organofluorine compounds, because functionalized fluorinated organic compounds are crucial in our daily life [1–9]. In particular, the transformation of perfluoro organic compounds is an efficient and economical method for the preparation of highly functionalized organofluorine compounds. Trifluorovinyl compounds, such as α,β,β -trifluorostyrene and their derivatives, have attracted increased attention, since they are regarded as a potential monomer for the preparation of polymers with a perfluorinated main chain [10–12]. Nevertheless, conventional methods for their preparation have thus far not been fully established. For instance, most of the initial preparation routes for trifluorostyrenes required multistep reactions [13–16]. A few reactions substituting the fluorine atom on fluoroolefines, including tetrafluoroethylene (**1**; TFE), with a carbon nucleophile are considered classic procedures [17–23]. These reactions involve an addition-elimination mechanism, and they often suffer from undesired side-reactions, such as a multi-substitution reaction, even at low reaction temperatures [17,19]. Pd(0)-catalyzed cross-coupling reactions of trifluorovinylzinc, tin, or borate reagents emerged in the 1980s as more direct synthetic methods [24–33]. A synthetic route involving a more stable trifluorovinyl borate has recently been developed to replace the zinc or tin reagents [34,35]. Alternative routes to synthesize (α,β,β -trifluoro)styrenes via the cross-coupling of chlorotrifluoroethylene with arylboronic acids have recently been reported [36,37]. Against such a background, we started developing a novel strategy for their preparation from **1**, because **1** is an economical bulk organofluorine feedstock for the production of poly(tetrafluoroethylene) and co-polymers with other alkenes [38–40]. However, to the best of our knowledge, no catalytic reactions involving **1** had been reported until we reported the first catalytic transformation reaction [41], while homogeneous catalytic reactions involving C–F bond activation have received an increasing amount of attention [42–53]. The C–F bond activation reaction of **1** had been achieved only in a few stoichiometric reactions [54–56]. In a groundbreaking study of C–F bond activation in **1**, Kemmit reported that LiI promoted the oxidative addition of **1** to platinum(0) [54]. This observation inspired us to develop a palladium-catalyzed cross-coupling reaction using **1** with organometallic compounds.

This review is the first report of the formation, structure and reactivity of a trifluorovinyl palladium(II) complex from the oxidative addition of the C–F bond of **1** to palladium(0) in the presence of LiI. The first palladium-catalyzed cross-coupling reaction of **1** with aryl zinc compounds in the presence of LiI is also discussed [41,57]. We then discuss the development of the active Pd(0)/PR₃ species that enabled the oxidative addition of the C–F bond of **1** using no additives. By employing the Pd(0)/PR₃ species as a catalytic precursor, a Suzuki-Miyaura type of a cross-coupling reaction of **1** with arylboronates was successfully achieved [58]. This cross-coupling reaction required neither an extraneous base to enhance the reactivity of organoboron reagents nor a Lewis acid to promote the oxidative addition of a C–F bond.

The transformation of perfluoroarenes into highly functionalized perfluoroaryl-substituted compounds is also an efficient and economical strategy. Radius *et al.* reported a coupling reaction of octafluorotoluene (C₇F₈) and decafluorobiphenyl (C₁₂F₁₀) with arylboronic acid in the presence of a catalytic amount of NHC-nickel(0) catalyst (where NHC represents *N*-Heterocyclic carbene) [59]. This group also demonstrated the usefulness of a NHC-nickel(0) complex for the C–F bond activation of

hexafluorobenzene (C_6F_6), and the $Ni(0)/NHC$ complex did indeed show catalytic activity toward the hydrodefluorination of C_6F_6 [60–62]. However, an efficient catalytic transformation of C_6F_6 involving a C–C bond formation is very rare. To the best of our knowledge, only two examples of transition metal-catalyzed C–C bond formation reactions using C_6F_6 to give biaryls have been reported [63,64]. Yoshikai and Nakamura reported the coupling reaction of multi-fluorinated benzenes with aryl zinc catalyzed by a nickel catalyst ligated with alkoxydiphosphine, and that group also achieved the selective activation of a C–F bond [64]. From a practical point of view, nonetheless, there remains no easily accessible catalyst system that is applicable for a coupling reaction that could introduce a perfluorinated aryl group to a certain position of arene compounds. We know the synergistic effect of $Pd(0)$ and lithium iodide has been successfully applied to the C–F bond cleavage of C_6F_6 , and the first development of the $Pd(0)$ -catalyzed cross-coupling reaction of C_6F_6 with diarylzinc has been achieved [65]. This review introduces a possible reaction path based on certain stoichiometric reactions and on the robustness of $trans-(PCy_3)_2Pd(I)(C_6F_5)$ formed by the oxidative addition of C_6F_6 to $Pd(PCy_3)_2$ in the presence of LiI .

2. Results and Discussion

2.1. $Pd(0)$ -Catalyzed Cross-Coupling Reactions of Tetrafluoroethylene with Diarylzinc Reagents

The treatment of LiI with $(\eta^2-CF_2=CF_2)Pd(PPh_3)_2$ (**2a**) in THF at room temperature promoted the oxidative addition of a C–F bond of THF to give a trifluorovinyl palladium(II) iodide (**3**; Scheme 1). In contrast to the known platinum analog, $(\eta^2-CF_2=CF_2)Pt(PPh_3)_2$ [54], the C–F bond cleavage on palladium took place with no heating of the reaction mixture. An attempt to cleave the carbon-fluorine bond in **2a** at 100 °C in the absence of LiI resulted in the decomposition of **2a** along with the liberation of a TFE molecule and the precipitation of Pd black. Thus, cleavage of the C–F bond, generating **3**, required LiI to act as a Lewis acid to enhance the elimination ability of fluorine. The formation of a strong $Li-F$ bond might also be important for oxidative addition at room temperature. The ORTEP drawing of **3** definitely shows that the palladium in **3** adopted a square-planar coordination geometry and was coordinated with two PPh_3 ligands in a *trans* manner (Figure 1). Complex **3** is the first example of a mononuclear trifluorovinyl complex generated by the carbon-fluorine bond cleavage of **1** with a well-defined structure [53,66].

Scheme 1. C–F bond cleavage of **1** on palladium.

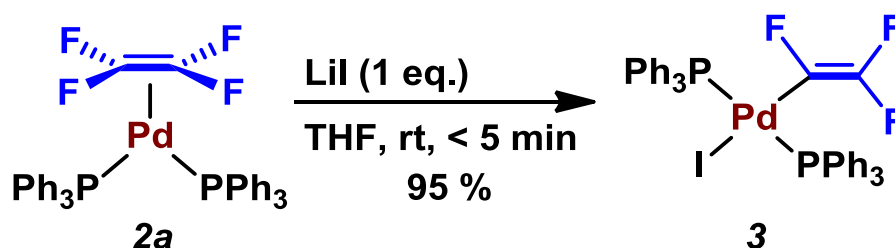
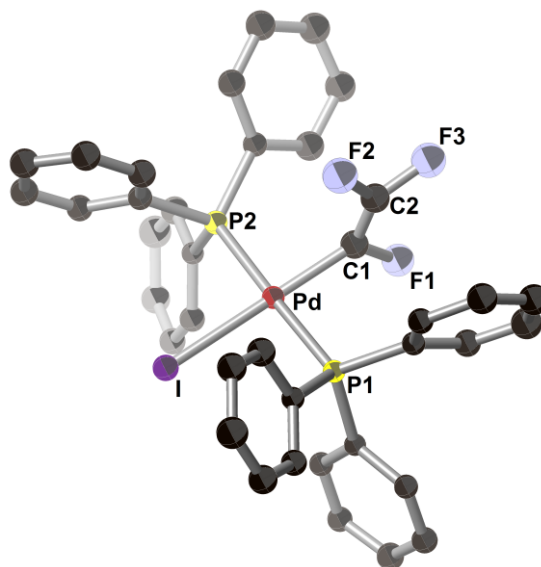


Figure 1. Molecular structure of **3** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity.



Complex **3** seemed to be a promising reaction intermediate for the preparation of various trifluorovinyl compounds via cross-coupling reactions of TFE with organometallic reagents. In particular, each reaction step in the cross-coupling of TFE with arylmetal reagents to give trifluorovinylarenes had to occur at a relatively low temperature, since the undesired side-reactions of the resultant trifluorovinylarenes gave a complex mixture. In fact, the [2 + 2] cyclodimerization of (α,β,β -trifluoro)styrene occurred in a head-to head manner at 80 °C to give a mixture of *cis* and *trans* isomers [27,67]. Therefore, **3** was reacted with a stoichiometric amount of ZnPh_2 (**4a**) to determine if the expected reaction would occur at room temperature to give (α,β,β -trifluoro)styrene (**5a**). Although the reaction of **3** with 0.5 equiv of **4a** in THF resulted in the formation of a complicated mixture that contained a small amount of the expected compound **5a**, in the presence of LiI and DBA (*trans,trans*-dibenzylideneacetone), the reaction of **3** with **4a** proceeded smoothly to give **5a** in 87% yield (Scheme 2). Both LiI and DBA are potential additives in the cross-coupling reaction, since the reaction of TFE with $\text{Pd}_2(\text{dba})_3$ and PPh_3 in the presence of LiI, giving **3**, simultaneously yielded an uncoordinated DBA. The role of lithium iodide in this reaction was the formation of reactive zincates such as $\text{Li}[\text{ArZnXI}]$ ($X = \text{Ar}$ or I , *vide infra*) [68]. By contrast, platinum is an unlikely catalyst for the cross-coupling reaction, because the oxidative addition of TFE to platinum(0) requires both a much higher temperature and a longer reaction time (at 95 °C for 24 h) [54].

A logical extension of this reaction scheme was to conduct a Pd-catalyzed coupling reaction of TFE with diarylzinc in the presence of LiI, and the results are summarized in Table 1. In the presence of 2.5 mol% of $\text{Pd}_2(\text{dba})_3$ and 10 mol % of PPh_3 , the coupling reaction of **1** with **4a**, which was prepared by treating ZnCl_2 with 2 equiv of PhMgBr *in situ*, took place at room temperature. The desired product **5a** was obtained in 48% yield (entry 1). Under the same reaction conditions, the reaction with isolated ZnPh_2 occurred somewhat slowly compared with ZnPh_2 prepared *in situ* (entry 2). As expected from the stoichiometric reactions, the addition of lithium iodide was essential for the Pd-catalyzed coupling reaction (entry 3). Although either elongation of the reaction time or elevation of the reaction temperature was required, even with reduced catalyst loading (0.01 mol% of $\text{Pd}_2(\text{dba})_3$), the catalytic

reaction proceeded smoothly at 40 °C to give **5a** in 72% yield (entry 4). The rate of the coupling reaction was remarkably enhanced by the omission of PPh₃ from the catalytic system, and **5a** was obtained in 73% yield (entry 5). By contrast, in the absence of Pd(0), the reactions of **1** with **4a** were negligible, indicating that Pd(0) catalyzed the coupling reaction with or without lithium iodide (entries 6 and 7).

Scheme 2. Reactions of **3** with ZnPh₂ (**4a**) in the presence of additives.

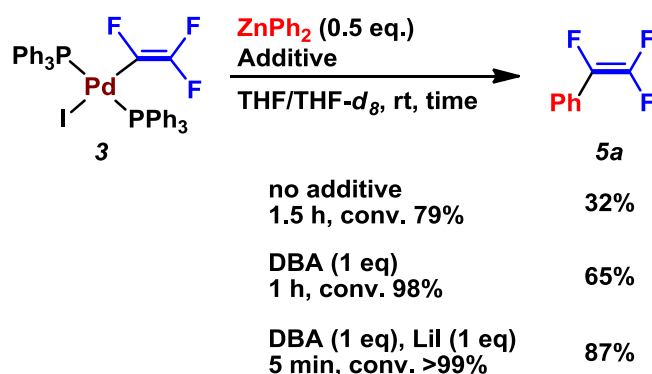
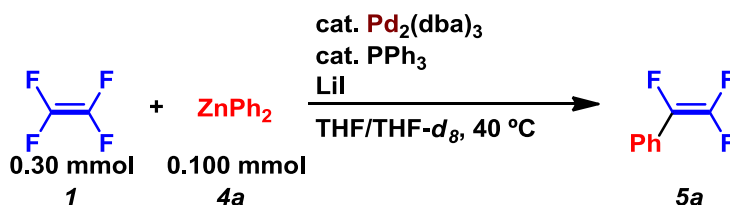


Table 1. Optimization of the reaction conditions for the Pd(0)-catalyzed cross-coupling reaction of **1** with **4a**. General conditions: solvent; 0.5 mL. All reactions were conducted in a pressure-tight NMR tube. Yields, based on aryl group, were determined by ¹⁹F NMR analysis of the crude product using α,α,α-trifluorotoluene as an internal standard.

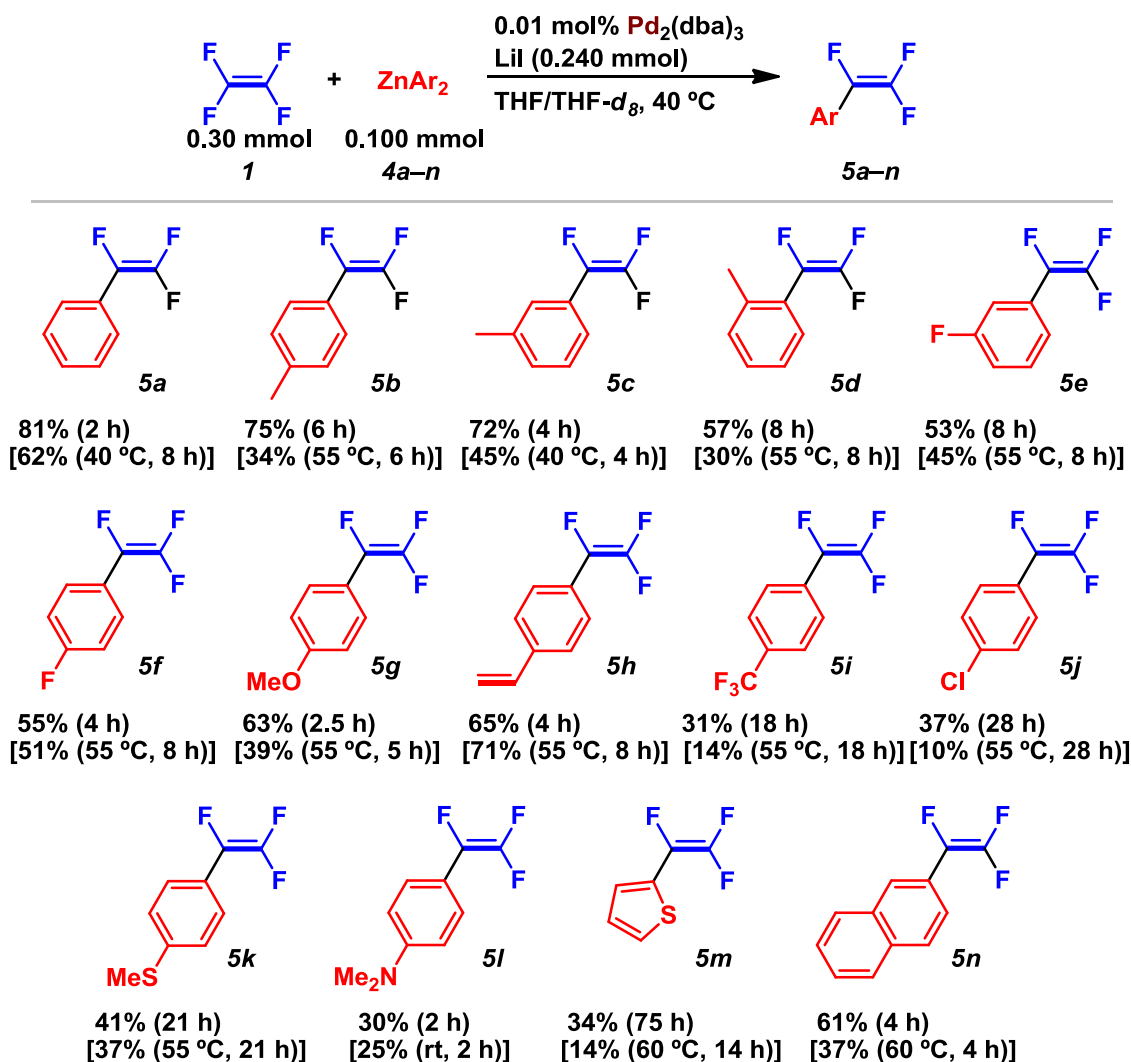


| Entry | Pd ₂ (dba) ₃ /mol% | PPh ₃ /mol% | Preparation of ZnPh ₂ (4a) | Lil/mmol | Time/h | Yield/% |
|-------|--|------------------------|--|----------|--------|---------|
| 1 | 2.5 | 10.0 | ZnCl ₂ + 2 PhMgBr | — | 24 | 48 |
| 2 | 2.5 | 10.0 | isolated ZnPh ₂ | — | 24 | 19 |
| 3 | 2.5 | 10.0 | ZnCl ₂ + 2 PhMgBr | 0.240 | 9 | 61 |
| 4 | 0.01 | 0.04 | ZnCl ₂ + 2 PhMgBr | 0.240 | 24 | 72 |
| 5 | 0.01 | — | ZnCl ₂ + 2 PhMgBr | 0.240 | 4 | 73 |
| 6 | — | — | ZnCl ₂ + 2 PhMgBr | 0.240 | 24 | 3 |
| 7 | — | — | ZnCl ₂ + 2 PhMgBr | — | 24 | 9 |

The scope of diarylzinc reagents was investigated using the optimized reaction conditions (Scheme 3). The treatment of **1** with **4a**, which was prepared by the reaction of ZnCl₂ with PhMgCl, gave **5a** in 81% yield, which marked the highest reactivity from among the arylzinc reagents (TON = 8100, entry 9). In addition, the reactions with Zn(4-Me-C₆H₄)₂ (**4b**) and Zn(3-Me-C₆H₄)₂ (**4c**) gave the monoaryl-substituted products **5b** and **5c** in 75% and 72% yields, respectively, while the reaction with Zn(2-Me-C₆H₄)₂ (**4d**) gave only 57% yield of **5d**. The reactions with fluoro-substituted aryl zinc reagents (**4e** and **4f**) yielded the corresponding products (**5e** and **5f**) in 53% and 55% yields, respectively. The reactions with *p*-substituted arylzinc reagents, such as Zn(4-MeO-C₆H₄)₂ (**4g**) and

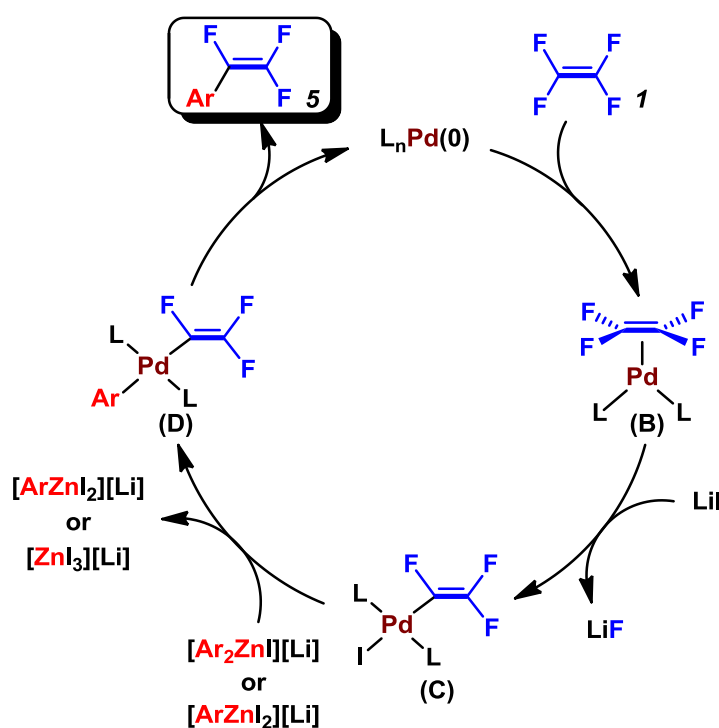
Zn(4-styryl)₂ (**4h**), also afforded the corresponding products (**5g** and **5h**) in good yields. By contrast, Zn(4-CF₃-C₆H₄)₂ (**4i**), Zn(4-Cl-C₆H₄)₂ (**4j**) and Zn(4-MeS-C₆H₄)₂ (**4k**) required prolonged reaction times to yield the corresponding products (**5i–k**) in moderate yields. In addition, the reaction with Zn(4-Me₂N-C₆H₄)₂ (**4l**) was terminated within 2 hours, and as a consequence, the yield of the desired product (**5l**) remained at 30%. Use of Zn(2-thienyl)₂ (**4m**) allowed the reaction with **1** to proceed to give **5m**, although much longer reaction time was required and the product yield was low. This catalytic system was also successfully applied to Zn(2-naphthyl)₂ (**4n**), which gave the corresponding product (**5n**) in 61% yield. The reaction products were isolated as a THF solution due to the occurrence of the cyclodimerization to give hexafluoro-cyclobutane derivatives at a higher concentration [69]. Relatively lower isolated yields were caused either by high volatility even at room temperature or by cyclodimerization.

Scheme 3. Pd(0)-Catalyzed Coupling Reaction of TFE (**1**) with ZnAr₂ (**4**). General conditions: **1** (3.5 atm, >0.30 mmol, estimated from an equation of state), **4** (0.100 mmol, *in situ* prepared by treating of ZnCl₂ with 2 equiv of ArMgBr), solvent; 0.5 mL. All reactions were conducted in a pressure-tight NMR tube. Yields, based on aryl group, were determined by ¹⁹F NMR analysis of the crude product using α,α,α-trifluorotoluene as an internal standard. The values in parentheses are of isolated yield.



Based on the results described above, the Pd-catalyzed monoaryl substitution reaction of **1** might proceed via the mechanism depicted in Scheme 4. Coordination of a TFE molecule to Pd(0) would take place to generate an η^2 -TFE species (**B**). Then oxidative addition of a C–F bond to Pd(0) is promoted by lithium iodide, generating a trifluorovinyl palladium(II) intermediate (**C**). Transmetalation of **C** with Li[ArZnXI] would yield a transient aryl palladium intermediate (**D**), which would undergo reductive elimination to afford (α,β,β -trifluoro)styrene derivative **5** along with regeneration of the Pd(0) species. The addition of lithium iodide is essential not only for accelerating cleavage of the carbon-fluorine bond, but also for enhancing the reactivity of arylzinc reagents via the formation of zincates, such as Li[ArZnXI].

Scheme 4. A plausible reaction mechanism.



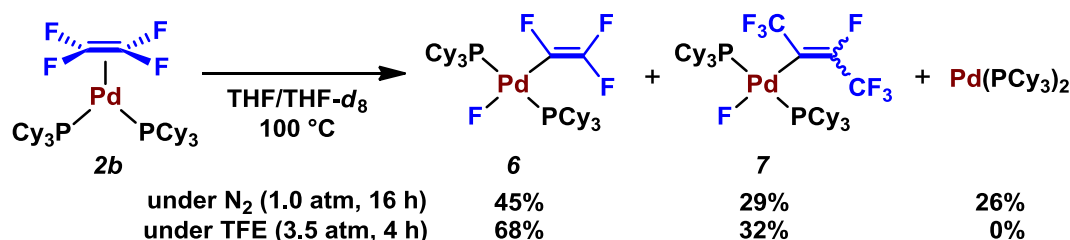
2.2. Pd(0)-Catalyzed Cross-Coupling Reactions of Tetrafluoroethylene with Arylboronates

Our next concern was to apply the $C(sp^2)$ –F bond activation methodology to a Suzuki-Miyaura type C–C bond formation reaction that generally offers the advantages of tolerance across a broad range of functional groups [70–74]. Most of the reported Suzuki-Miyaura type cross-coupling reactions via C–F bond cleavage, employing either highly electron-deficient organofluorine compounds or those bearing a directing group, have traditionally been conducted in the presence of a base [59,75–85], whereas fluoride anion itself is regarded as a good activator for neutral organoboron reagents. The role of a base in a Suzuki-Miyaura coupling reaction is generally considered to follow one of two patterns; either converting a neutral organoboron compound into a nucleophilic boronate, or converting a palladium halide intermediate into an active palladium species via a ligand exchange reaction by the base [86,87]. In fact, Widdowson pointed out the possibility that the use of an extraneous base should be, in principle, catalytic [75]. Such a reaction, however, has not been developed. Some coupling reactions with organoboron reagents are known to proceed under neutral conditions, in which such an

active species as palladium alkoxy or acyl complex is generated *in situ* via the oxidative addition of a C–O bond [75,88,89]. We speculated that if the transition-metal fluorides generated via C–F bond cleavage would have reactivity sufficiently high so as to act as a fluoride donor, the development of base-free C–C couplings with organoboron reagents would bring a significant concept to the Suzuki–Miyaura coupling reaction with organofluorine compounds. Thus, we started developing a base-free C–C bond formation reaction of **1** with arylboronates in the presence of a Pd(0) catalyst.

We began by seeking an active species that could cleave the C–F bond of **1** without additives, because our original protocol using LiI eliminated the chance to generate a transition-metal fluoride intermediate in return for efficient C–F bond cleavage [41,54–56,90]. As a result, the thermolysis of $(\eta^2\text{-CF}_2\text{=CF}_2)\text{Pd}(\text{PCy}_3)_2$ (**2b**) in THF at 100 °C under a N₂ atmosphere underwent a C–F bond activation of **1** to give an expected trifluorovinylpalladium(II) fluoride (**6**) in 45% yield (Scheme 5). NMR observation revealed the concomitant formation of a palladium 2-perfluorobutenyl species (**7**) as well as Pd(PCy₃)₂. Complex **7** was identified on the basis of the similarity of the ¹⁹F NMR patterns observed in perfluoro-2-butenyl zinc species, CF₃(ZnX)C=CFCF₃ [91]. The recovery of Pd(PCy₃)₂ (26%) indicated the existence of a coordination-dissociation equilibrium of **1** to palladium under the reaction conditions. Therefore, this reaction was carried out under a TFE atmosphere (1 atm), leading to an improvement in the yield of **6**. By contrast, as already mentioned above, the corresponding palladium fluoride analog could not be generated at all by heating the PPh₃ analog **2a** [41]. In the ¹⁹F NMR spectrum of **6**, characteristic upfield-shifted resonance attributable to a fluorine adjacent to palladium appeared at –317.9 ppm. To the best of our knowledge, the examples of fluoropalladium complexes generated via the oxidative addition of a C–F bond are very rare [82,92–94]. In addition, complex **6** marked the first example of a structurally well-defined oxidative addition product of **1** on a transition metal without the use of Lewis acid additives.

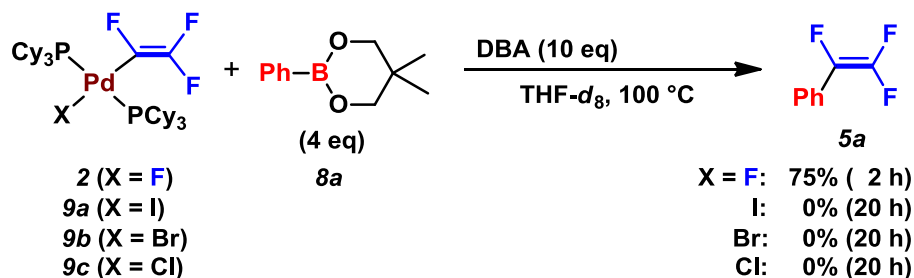
Scheme 5. Generation of trifluorovinylpalladium(II) fluoride via C–F bond cleavage of **1**.



We next examined the reaction of **6** with a stoichiometric amount of 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**8a**) to evaluate the degree of its reactivity toward organoborane reagents. The treatment of **6** with 4 equiv of **8a** in the presence of DBA at 100 °C for 2 h afforded **5a** in 75% yield (Scheme 6). In contrast, no C–C bond formation occurred, even for a prolonged reaction time, when **8a** was treated with the corresponding palladium iodide (**9a**) that reacts with **4a**. In addition, neither the corresponding palladium bromide (**9b**) nor chloride (**9c**) underwent a coupling reaction with **8a**. These observations clearly show that the C–C bond formation with organoboron reagents is unique to palladium fluoride **6** among corresponding palladium halides. In fact, the Pd(0)-catalyzed coupling reaction of chlorotrifluoroethylene with **8a** in the absence of a base gave no coupling products, probably due to the generation of the unreactive trifluorovinylpalladium chloride intermediate. As

mentioned above, the Pd-catalyzed coupling reaction of chlorotrifluoroethylene with arylboronic acids in the presence of a base has been reported [36,37].

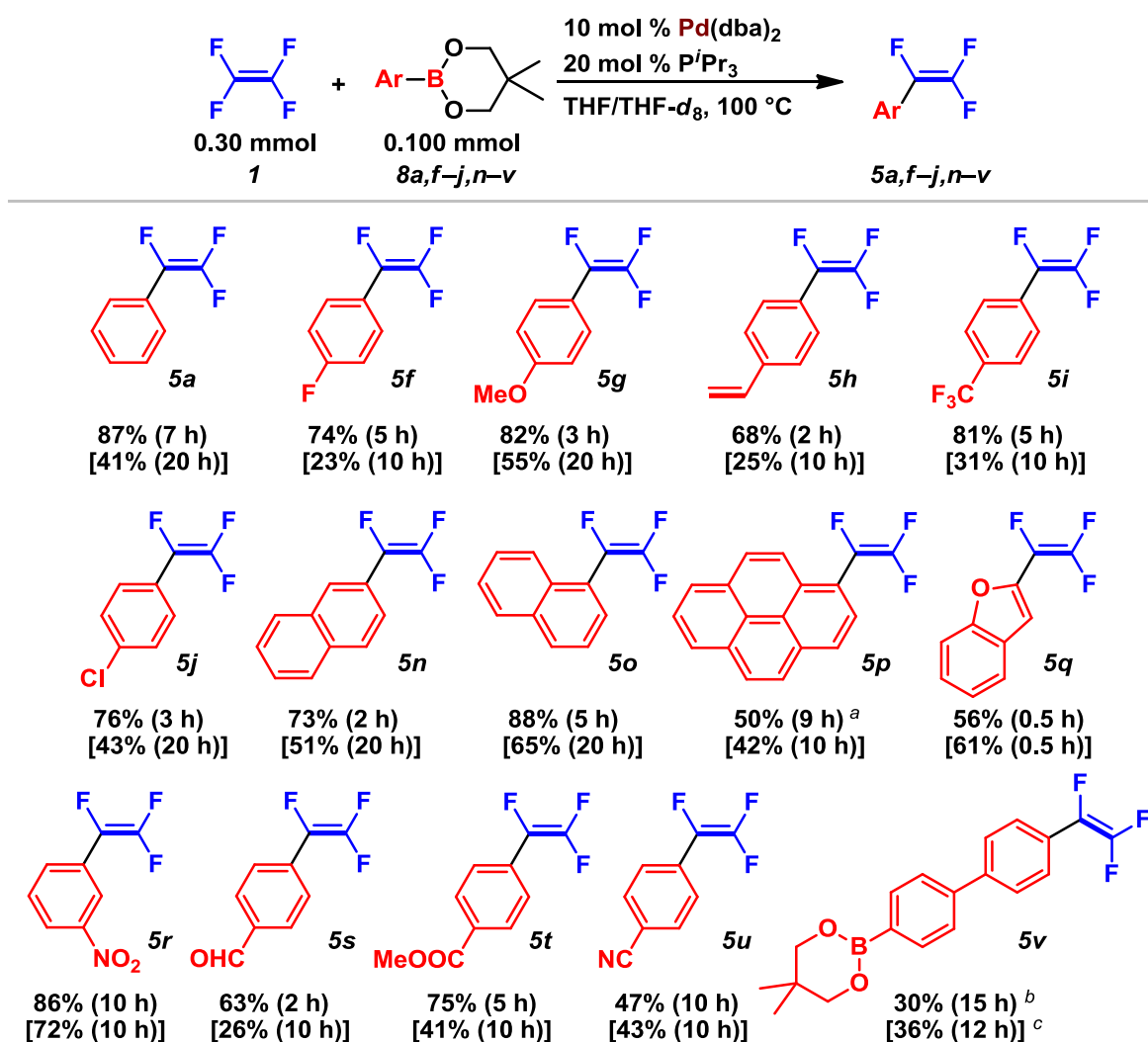
Scheme 6. Reactivity of palladium trifluorovinyl halides towards **8a**.



It seemed logical to apply this reaction scheme to a palladium-catalyzed cross-coupling reaction of **1** with **8a**. In the presence of 10 mol % Pd(dba)₂ and 20 mol % PCy₃, the coupling reaction of **1** with **8a** proceeded at 100 °C, in the absence of any additive, to afford **5a** in 66% yield. This result pointed out that the reaction takes place even in the absence of a base, while the use of a base is generally indispensable for the Suzuki-Miyaura coupling reaction to enhance the reactivity of organoboron reagents. The addition of CsCO₃ did not affect the yield of **5a**. Further optimization of the cross-coupling reaction of **1** with **8a** was carried out, and as a result, the reaction conducted at 100 °C in the presence of Pd(dba)₂/P^{*i*}Pr₃ in THF led to the formation of the desired product **5a** in 83% yield [95].

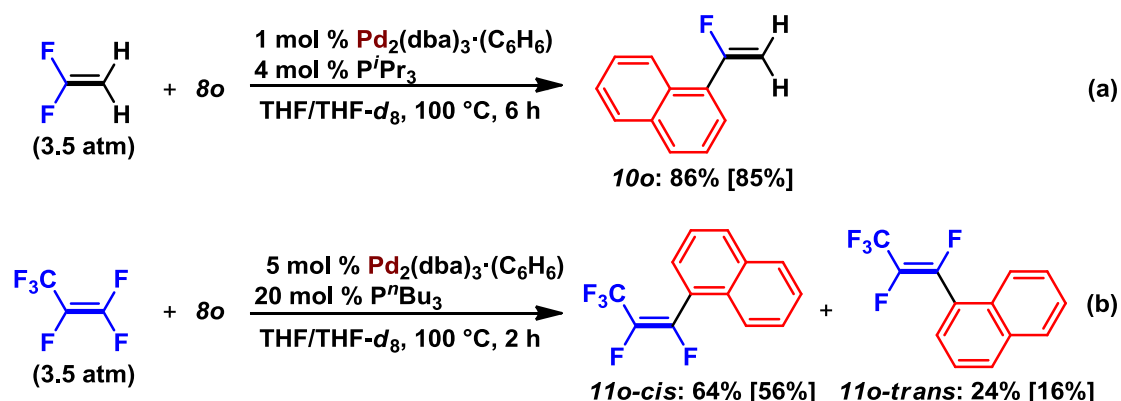
The optimized reaction conditions were used to investigate the scope of the cross-coupling reaction with arylboronates (Scheme 7). The reactions with 4-anisyl, 4-vinylphenyl, and 4-trifluoromethylphenyl boronates (**8g–i**) also afforded the corresponding trifluorostyrene derivatives (**5g–i**) in good to moderate yields. Of the 4-halogenophenyl boronates employed, 4-fluorophenyl and 4-chlorophenyl boronates yielded *p*-fluoro- and *p*-chloro-substituted (α,β,β-trifluoro)styrenes (**5f** and **5j**) in 74% and 76% yields, respectively. In contrast, no coupling product was generated by employing 4-bromophenyl boronate, probably due to the occurrence of an undesired oxidative addition of the C–Br bond. In addition, the reactions with 2- and 1-naphthyl boronates (**8n** and **8o**) gave **5n** and **5o** in 73% and 88% yields, respectively. Furthermore, the reaction with 1-pyrenyl boronates (**8p**) gave **5p** in moderate yield. The reactions with 2-benzofulyl boronates (**8q**) yielded the corresponding products (**5q**) in moderate yield. Although this catalytic reaction leaves much to be desired regarding the catalyst loading and the product yield, it is of great significance in preparing substituted trifluorostyrenes bearing nitro, aldehyde, ester, and cyano groups (**5r–u**). These functional groups can easily react with Grignard reagents that are required for the *in situ* preparation of organozinc reagents, and therefore, products **5r–u** were difficult to synthesize from a coupling reaction with organozinc reagents. In addition, bis-boronate reagents, such as 4,4'-biphenyl diboronate (**8v**), can be used to prepare monotrifluorovinyl compounds, for which the unreacted boronate moiety was applied in a further cross-coupling reaction to synthesize highly-functionalized derivatives.

Scheme 7. Pd(0)-catalyzed base-free cross-coupling reaction of **1** with arylboronates (**8**). General conditions: **8** (1.00 mmol), solvent (10.0 mL), TFE (3.5 atm). Yields were determined by ^{19}F NMR analysis of the crude product using α,α,α -trifluorotoluene as an internal standard. The values in brackets are of isolated yields. ^a Using P^iPr_3 instead of P^tPr_3 ; ^b Reaction conditions: **8v** (0.30 mmol), solvent (1.5 mL), TFE (30 mg, 0.30 mmol). NMR analysis revealed that 29% of **8v** was remained and the bistrifluorovinyl compound was generated in 7% yield; ^c Reaction conditions: **8v** (0.95 mmol), solvent (10.0 mL), TFE (100 mg, 1.00 mmol). After the isolation procedure, 130 mg (36%) of **8v** was recovered and the bistrifluorovinyl compound was isolated in 10% yield.



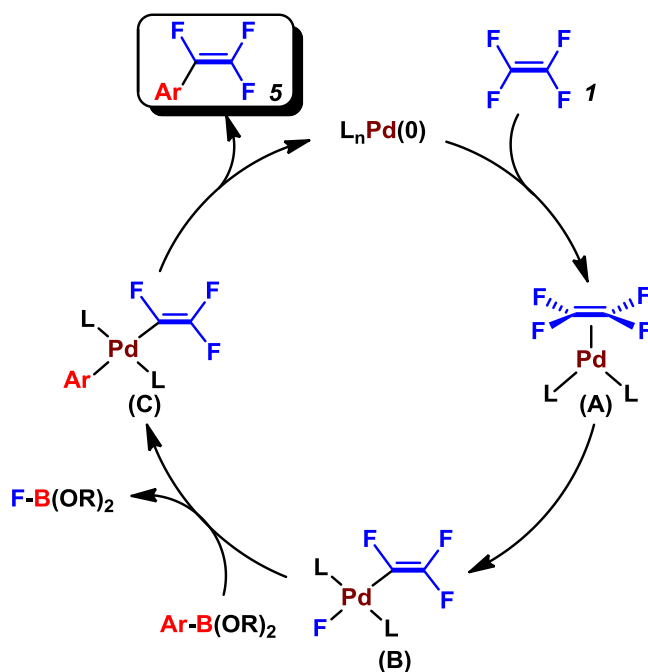
This base-free cross-coupling reaction with arylboronates can be successfully expanded to other organofluorine molecules. The reaction of vinylidene fluoride with **8o** proceeded in the presence of Pd(0)/ P^tPr_3 catalyst, to give 1-(1-fluorovinyl)naphthalene (**10o**) in 86% yield (Scheme 8a). In addition, the corresponding reaction with hexafluoropropylene gave a mixture of regioisomers (**11o**) (Scheme 8b), while Dmowski reported the reaction of $\text{CF}_3\text{CF}=\text{CF}_2$ with PhMgBr to give an *E/Z* mixture of $\text{CF}_3\text{CF}=\text{CFPh}$ (*E/Z* = 83/17) [96]. However, a Pd(0) catalyst was ineffective in a base-free coupling reaction of fluoroarenes.

Scheme 8. Pd(0)-catalyzed base-free cross-coupling reactions of (a) vinylidene fluoride or (b) hexafluoropropylene with arylboronates **8o**. Yields were determined by ^{19}F NMR analysis of the crude product using α,α,α -trifluorotoluene as an internal standard. The values in brackets are of isolated yields.



The base-free Pd-catalyzed monoaryl substitution of **1** might proceed as follows (Scheme 9). Coordination of a TFE molecule to Pd(0) would take place to generate an η^2 -TFE species (A). Then, the combination of Pd(0) and trialkylphosphines with a strong σ -donor ability would enable the oxidative addition of a C–F bond to Pd(0) with no additives, generating a trifluorovinylpalladium(II) fluoride intermediate (B). The transmetalation of B with arylboronates [97], would give C, followed by reductive elimination, which would afford **5** along with a regeneration of the Pd(0) species and boronefluorides. Another possible mechanism involving concerted bimolecular elimination via a five-membered transient intermediate could afford **5** [98]. It should be emphasized that no extraneous base is required in this reaction, although extraneous base is generally requisite for the Suzuki-Miyaura cross-coupling reaction to promote a transmetalation step with organoboron reagents.

Scheme 9. A plausible reaction mechanism.

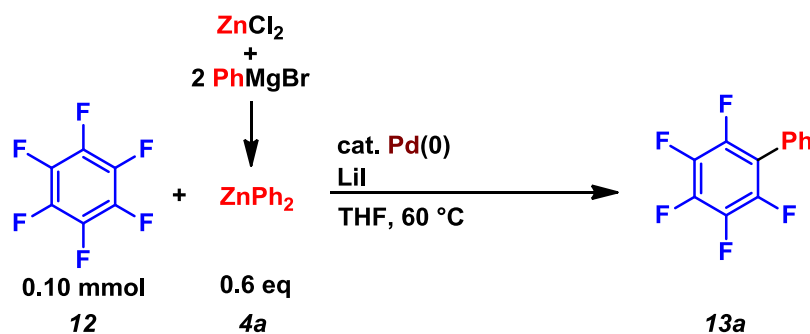


2.3. Pd(0)-Catalyzed Cross-Coupling Reaction of Perfluoroarenes with Diarylzinc Reagents

Next, we developed the coupling reaction of perfluoroarenes including hexafluorobenzene with diarylzinc compounds, since our methodology suggested the possibility of a cleavage of the unreactive C–F bond of C_6F_6 via the cooperation of Pd(0) and LiI. First, we simply applied the reaction conditions of the coupling reaction of TFE with Ar_2Zn to the coupling reaction of C_6F_6 (**12**) with Ar_2Zn (Table 2). In the presence of 5 mol % of $Pd_2(dba)_3$, 20 mol % of PPh_3 , and 2.5 equiv of LiI at 60 °C in THF, the reaction of **12** with **4a**, prepared *in situ* by reacting $ZnCl_2$ with 2 equiv of $PhMgBr$, gave a trace amount of pentafluorophenyl benzene (**13a**), and the **12** remained intact (entry 1). To promote the oxidative addition of **12** to palladium, $Pd(PCy_3)_2$ was examined as a catalyst precursor for the coupling reaction, and **13a** was obtained in 70% yield (entry 2). When isolated **4a** (purchased from Strem) was employed in the coupling reaction, **13a** was obtained in 63% yield (entry 3). Because a catalytic reaction using pentafluoroiodobenzene, C_6F_5I , as a substrate gave only a trace amount of **13a** (<5% yield, 70% S. M. recovered), we ruled out the possibility that C_6F_5I could be generated as a result of a nucleophilic attack reaction of iodide anion on **12**. In the absence of a palladium catalyst, no coupling product was observed (entry 4). An increase in the amount of LiI improved the yield of **13a** to 75% (entry 5), whereas in the absence of LiI, **13a** was obtained in 5% yield even after a prolonged reaction time (entry 6). This result contrasted with that from the reaction of **1** with **4a** generated *in situ* from $PhMgBr$ and $ZnCl_2$ (Table 1, entry 1) and indicated that the addition of LiI was crucial for the occurrence of the coupling reaction. In the presence of PCy_3 , $Pd(OAc)_2$ was also effective as a catalyst for the coupling reaction (entry 7). A mixture of $Pd_2(dba)_3$ and PCy_3 (5 and 20 mol % each) showed catalytic activity to give **13a** in 77% yield, while much more catalyst loading (10 mol % Pd(0)) was required for smooth progress in the coupling reaction (entry 8). Employing either DCPE (1,2-dicyclohexylphosphinoethane) or DCPB (1,4-dicyclohexylphosphinobutane) obviously retarded the desired coupling reaction (entries 9 and 10).

Scheme 10 summarizes the results of the Pd(0)-catalyzed cross-coupling reaction of perfluoroarenes with a variety of Ar_2Zn in the presence of LiI. Both (4-Me- C_6H_4) $_2Zn$ (**4b**) and (3-Me- C_6H_4) $_2Zn$ (**4c**) reacted with **12** to give the corresponding coupling products (**13b**, **13c**) in 70% and 53% yields, respectively. In contrast, no coupling reaction product was obtained from the reaction with $Zn(2-Me-C_6H_4)_2$ (**4d**). The reaction with *p*-substituted arylzinc reagents using either an electron-donating or electron-withdrawing group, such as $Zn(4-F-C_6H_4)_2$ (**4f**), $Zn(4-MeO-C_6H_4)_2$ (**4g**), or $Zn(4-Me_2N-C_6H_4)_2$ (**4i**), afforded the coupling compounds (**13f**, **13g**, **13i**) in 66%, 76%, and 74% yields, respectively. When a thienyl group was introduced, the reaction gave 2-pentaphenylthiophene (**13m**) in 55% yield. The reaction of **12** with (2-naphthyl) $_2Zn$ (**4n**) under the same reaction conditions for 8 h gave 2-pentafluorophenylnaphthalene (**13n**) in 65% yield. The reactions with $Zn(3,5-F_2-C_6H_3)_2$ (**4w**) also yielded the corresponding coupling products (**13w**) in 49% yield. Other functionalized aryl zinc species prepared by Knochel's group [99], such as $LiCl \cdot (p-EtCOOC_6H_4)ZnI$ and $LiCl \cdot (p-NCC_6H_4)ZnI$, were successfully applied to the coupling reaction with C_6F_6 , giving the corresponding products (**13x**, **13y**) in moderate isolated yields.

Table 2. Optimization of the catalytic reaction of C₆F₆ (**12**) with **4a** in the presence of Pd(0) catalyst. Yields were estimated by GC (tetradecane was used as an internal standard).

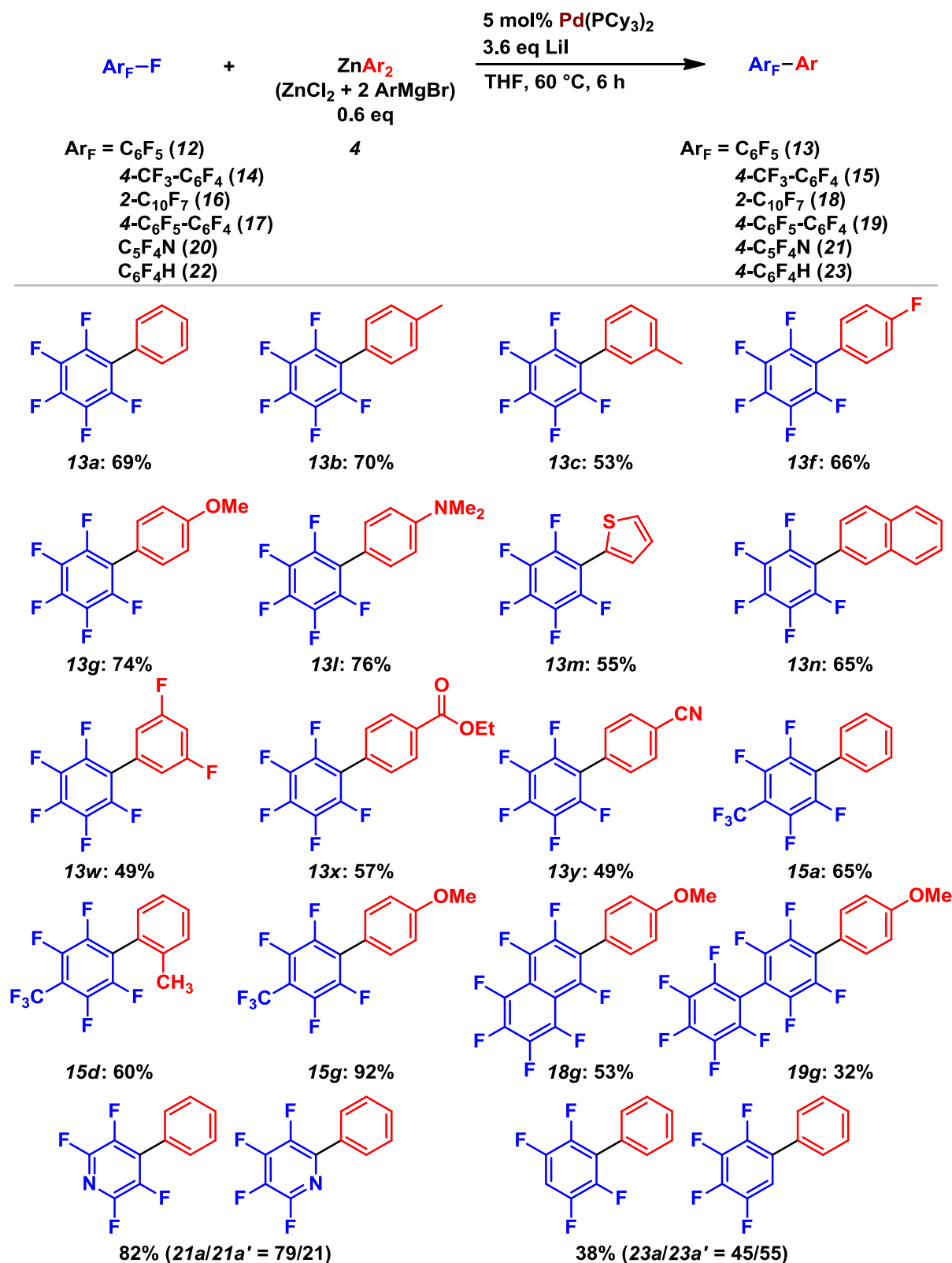


| Entry | Catalyst/mol% | Preparation of ZnPh ₂ (4a) | Lil/mmol | Time/h | Yield/% |
|-----------------|--|---------------------------------------|----------|--------|---------|
| 1 | Pd ₂ (dba) ₃ (5)/PPh ₃ (20) | ZnCl ₂ + 2 PhMgBr | 0.240 | 10 | trace |
| 2 | Pd(PCy ₃) ₂ (5) | ZnCl ₂ + 2 PhMgBr | 0.240 | 4 | 70 |
| 3 | Pd(PCy ₃) ₂ (10) | isolated ZnPh ₂ | 0.200 | 4 | 63 |
| 4 | — | ZnCl ₂ + 2 PhMgBr | 0.240 | 21 | — |
| 5 | Pd(PCy ₃) ₂ (5) | ZnCl ₂ + 2 PhMgBr | 0.360 | 6 | 75 |
| 6 | Pd(PCy ₃) ₂ (5) | ZnCl ₂ + 2 PhMgBr | — | 10 | 5 |
| 7 ^a | Pd(OAc) ₂ (5)/PCy ₃ (10) | ZnCl ₂ + 2 PhMgBr | 0.240 | 4 | 65 |
| 8 | Pd ₂ (dba) ₃ (5)/PCy ₃ (20) | ZnCl ₂ + 2 PhMgBr | 0.360 | 4 | 77 |
| 9 ^a | Pd(OAc) ₂ (5)/DCPE (5) | ZnCl ₂ + 2 PhMgBr | 0.240 | 9 | 13 |
| 10 ^a | Pd(OAc) ₂ (5)/DCPB (5) | ZnCl ₂ + 2 PhMgBr | 0.240 | 15 | trace |

^a 0.7 equiv of **4a** was employed.

The reaction was applicable to other perfluoroarenes. The coupling reaction of octafluorotoluene (C₇F₈; **14**) with **4a**, **4d**, and **4g** took place at the 4-position of **14** to give the corresponding products (**15a**, **15d**, **15g**) in good to excellent yields. In particular, the reaction of **14** with **4g** proceeded very smoothly, which allowed the confirmation of a back-ground reaction. In the absence of Pd(PCy₃)₂, **15g** was obtained in 30% yield at 60 °C for 6 h, which indicated that the palladium-catalyzed coupling reaction proceeded much faster than the background reaction. The use of perfluoronaphthalene (**16**) and perfluorobiphenyl (**17**) allowed the reaction with **4g** to give 2-(4-MeOC₆H₄)C₁₀F₇ (**18g**) and 4'-(4-MeOC₆H₄)C₁₂F₉ (**19g**) in 53% and 32% yields, respectively. In contrast, the reaction of perfluoropyridine (**20**) with **4a** afforded a mixture of tetrafluoro-4-phenylpyridine (**21a**) and tetrafluoro-2-phenylpyridine (**21a'**) in 65% and 17% yields, respectively. Pentafluorobenzene (**22**) also successfully participated in the coupling reaction with **4a**; however, the reaction product was obtained as a mixture of two regioisomers, 2,3,4,5-tetrafluorobiphenyl (**23a**) and 2,3,5,6-tetrafluorobiphenyl (**23a'**), and the combined yield of the coupling product was only 38%.

Scheme 10. Pd(0)-catalyzed base-free cross-coupling reaction of **1** with arylboronates (**8**). General conditions: Pd(PCy₃)₂ (0.05 mmol), **4** (0.60 mmol), LiI (2.40 mmol), solvent (5.0 mL), perfluoroarenes (1.00 mmol).



To gain deeper insight into the reaction mechanism, stoichiometric reactions of **12** with Pd(0) complexes were carried out. In a previous report by Grushin, the reaction of **12** with Pd(PCy₃)₂ in THF

at 70 °C for 24 h proceeded very slowly to yield a perfluorophenylpalladium(II) fluoride, *trans*-(PCy₃)₂Pd(F)(C₆F₅), in 3% yield [93]. In the presence of LiI, on the other hand, the oxidative addition took place much faster to give a perfluorophenylpalladium(II) iodide, *trans*-(PCy₃)₂Pd(I)(C₆F₅) (**24**), which indicated that an important role of lithium iodide was to accelerate the oxidative addition (Scheme 11a). Although the catalytic reaction of **12** with **4a** occurred in the presence of Pd₂(dba)₃ and 4 equiv of PCy₃ to give **13a** in 77% yield (Table 2, entry 7), an oxidative addition did not occur in the presence of DBA in the stoichiometric reaction at 60 °C (Scheme 11b). This result might have been due to an inhibition of the coordination of C₆F₆ to palladium by DBA under the stoichiometric reaction conditions and could indicate why Pd(PCy₃)₂ is a more efficient catalyst than the combination of Pd₂(dba)₃ and PCy₃. In stark contrast, even in the presence of LiI, the oxidative addition of C₆F₆ to Pd(PPh₃)₄ did not occur, which is consistent with the observation that no reaction occurred in the presence of PPh₃ (Table 2, entry 1). The ORTEP diagram of **24** definitely shows that the palladium in **24** adopts a square-planar coordination geometry and is coordinated with two PCy₃ ligands in a *trans* manner (Figure 2). A similar coordination geometry was observed in structurally well-defined Pd(II) complexes, such as *trans*-(PPh₃)₂Pd(Cl)(C₆F₅) and *trans*-(PCy₂R)₂Pd(I)(C₆F₅) (*R* = ferrocenyl group) [100,101].

Scheme 11. Stoichiometric Reactions of **12** with (a) Pd(PCy₃)₂ or (b) a mixture of Pd₂(dba)₃ and PCy₃ in the Presence of LiI.

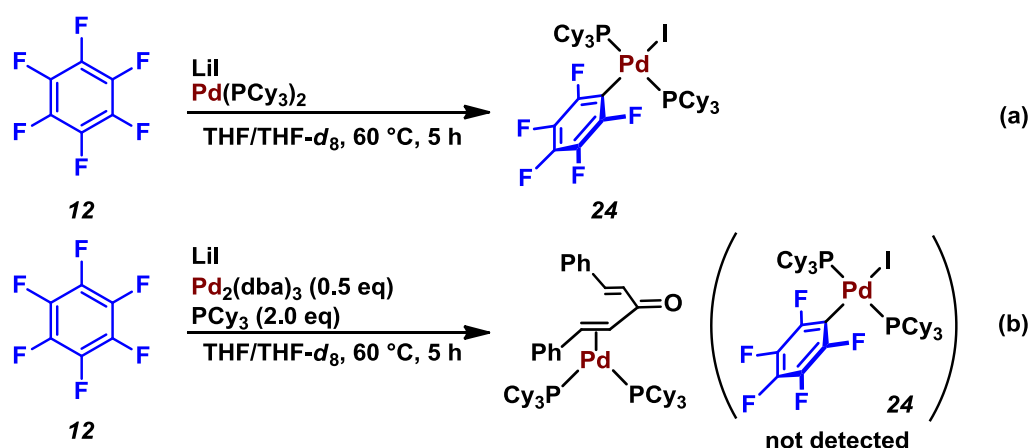
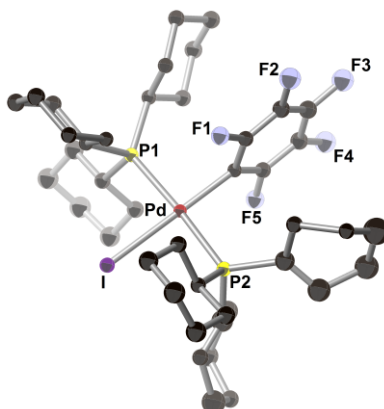


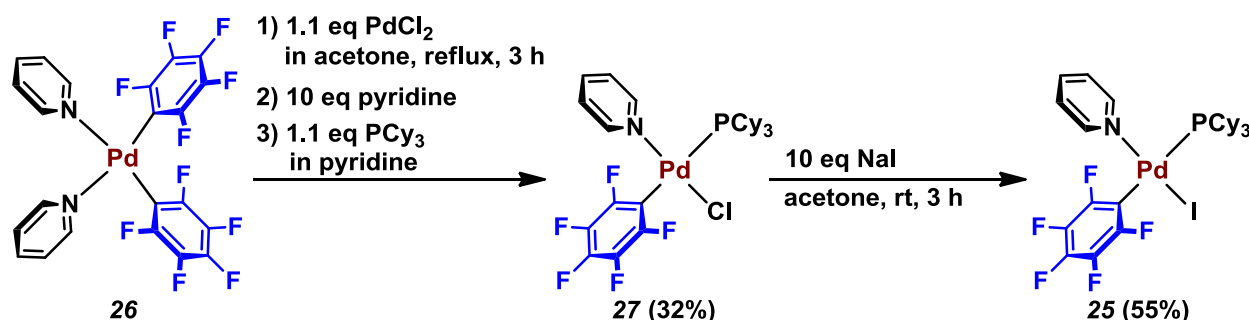
Figure 2. Molecular structure of **24** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity.



To confirm whether **24** is an intermediate in the Pd(0)-catalyzed cross-coupling reaction of **12** with diarylzinc or not, a stoichiometric reaction of **24** with **4a** was also carried out. As a result, only a yield of 5% of **13a** was obtained from a stoichiometric reaction conducted at 60 °C for 7 h in the presence of an excess amount of LiI, whereas **13a** was obtained under the catalytic reaction conditions mentioned above (60 °C for 6 h; Scheme 10). This result strongly indicates that **24** is an unlikely reaction intermediate due to the steric hindrance around the palladium center caused by the two bulkier PCy₃ ligands. Thus, we assumed that the oxidative addition of C₆F₆ to Pd(PCy₃)₂ in the presence of LiI might involve a dissociation process of the PCy₃ ligand to give a transient species, (PCy₃)Pd(C₆F₅)(I). The resultant 3-coordinated transient intermediate would undergo re-coordination of a PCy₃ ligand in the absence of **4a** to yield the thermodynamically favored, and unreactive **24**. On the other hand, in the presence of **4a**, transmetalation between the transient iodopalladium(II) species and **4a** took place smoothly to give the coupling product **13a**. These assumptions are consistent with the results from Hartwig's kinetic studies wherein the oxidative addition of chlorobenzene to Pd(PCy₃)₂, giving *trans*-(PCy₃)₂Pd(Ph)(Cl), involved the dissociation process of a PCy₃ ligand at the initial stage of the reaction [102]. Unfortunately, any attempt to prepare the transient intermediate failed due to its coordinative unsaturation, and therefore, *cis*-(C₆F₅)Pd(I)(py)(PCy₃) (**25**), in which pyridine acts as a labile ligand to generate a tentative 3-coordinate (PCy₃)Pd(C₆F₅)(I) species, was prepared as an alternative catalytic precursor.

Scheme 12 summarizes the synthetic route to the preparation of **25**. The reaction of (C₆F₅)₂Pd(Py)₂ (**26**) with PdCl₂ in acetone [103,104] followed by treatment with PCy₃ in pyridine resulted in the formation of *cis*-(C₆F₅)(Cl)Pd(Py)(PCy₃) (**27**) in 32% yield. Substitution of an iodide for the chloride ligand in **27** was accomplished by treating an acetone solution of **27** with an excess amount of NaI, giving the desired palladium(II) iodide **25** in 55% yield. The novel pentafluorophenyl palladium(II) iodide **25** was characterized on the basis of NMR spectroscopy and elemental analysis, as well as X-ray diffraction analysis. Both pyridine and PCy₃ ligands in **25** were situated in a mutual *cis* position with a square-planar Pd(II) geometry, as shown by X-ray diffraction (Figure 3).

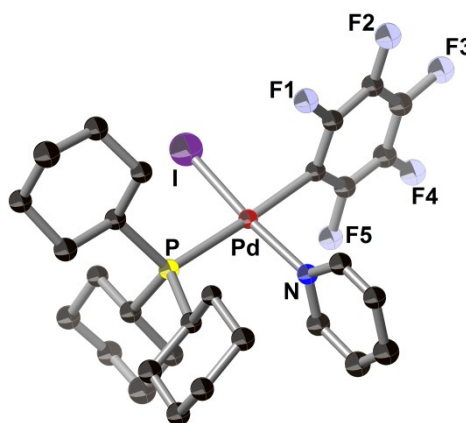
Scheme 12. Preparation of *cis*-(C₆F₅)Pd(I)(py)(PCy₃) (**25**).



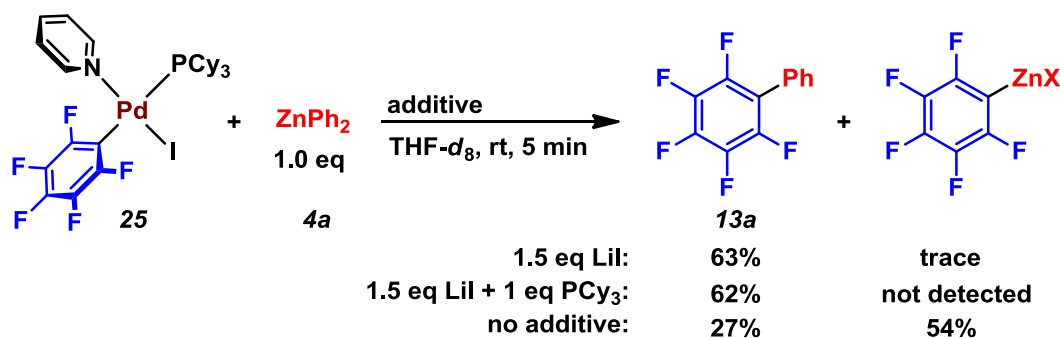
We then evaluated the reactivity of **25** toward **4a** in the presence or absence of lithium iodide. In the presence of LiI (1.5 equivalent), **25** reacted smoothly with **4a**, which was carefully purified by sublimation prior to use, in THF at room temperature to afford **13a** in 63% yield as a sole product (Scheme 13). The addition of PCy₃ to this reaction mixture affected neither the yield nor the selectivity of the reaction product. On the other hand, in the absence of LiI, the reaction of **25** with **4a** under the

same reaction conditions afforded a pentafluorophenylzinc species, C_6F_5ZnX ($X = I$ or C_6F_5), as a major product (54%), and **13a** was concomitantly obtained as a minor product in 27% yield. These observations suggest the following: (a) a transient $(PCy_3)Pd(C_6F_5)(I)$ species, generated via dissociation of the labile pyridine ligand of **25**, could be crucial for the smooth occurrence of transmetalation between the palladium(II) species and **4a**, and (b) the existence of LiI is essential for selective transmetalation to generate **13a**.

Figure 3. Molecular structure of **25** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity.



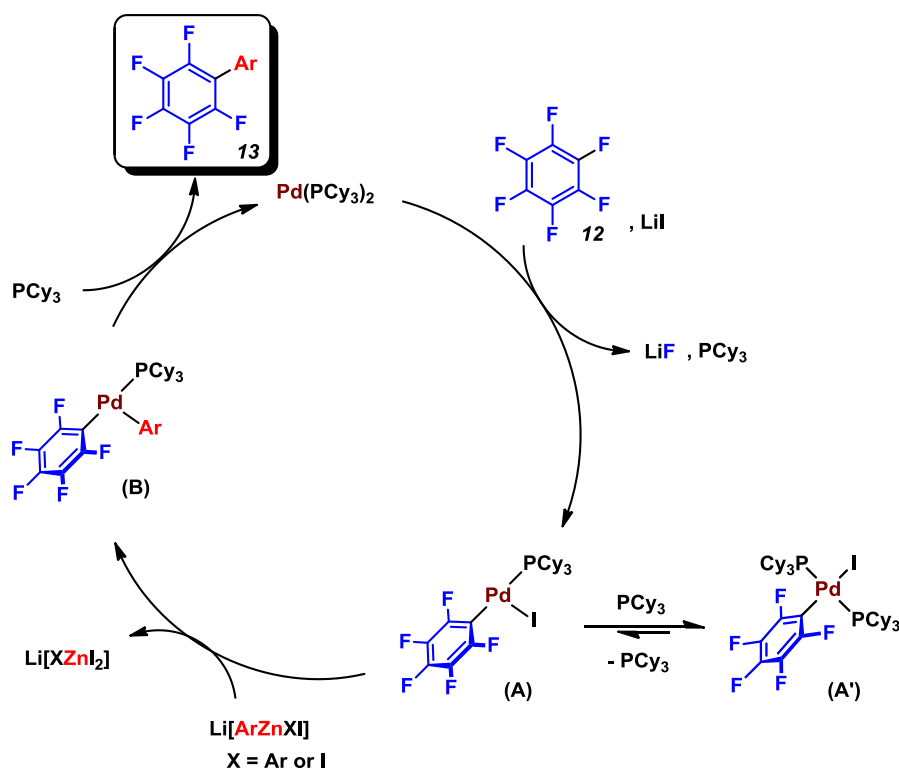
Scheme 13. Stoichiometric Reactions of **25** with **4a** in the presence or absence of LiI.



Based on those results, a plausible reaction mechanism was proposed, as shown in Scheme 14. In the presence of LiI, the oxidative addition of the C–F bond in **12** to Pd(0) would occur by dissociation of a PCy_3 ligand, forming a $(C_6F_5)(I)Pd(PCy_3)$ intermediate (**A**). We speculate that the LiI-promoted C–F bond activation of **12** on $Pd(PCy_3)_2$ would take place to give the *cis*-oxidative addition product, and the rapid dissociation of a PCy_3 ligand then might occur due to the steric hindrance of the two bulkier PCy_3 ligands. On the basis of theoretical and experimental studies, Radius *et al.* assumed that a related C–F bond activation of **12** on a $Ni(NHC)_2$ fragment, yielding *trans*- $[Ni(NHC)_2(C_6F_5)(F)]$, would proceed via the corresponding *cis*-oxidative addition product [61]. Transmetalation between **A** and **4** in the presence of LiI would take place to give a biaryl palladium(II) intermediate (**B**). This transmetalation step would progress in preference to the re-coordination of a PCy_3 ligand, giving an unreactive *trans*- $(PCy_3)_2Pd(C_6F_5)(I)$ (**A'**). The role of LiI in this reaction step might be rationalized by the formation of a reactive zincate such as $Li[ArZnXI]$ ($X = Ar$ or I) that would enable the efficient

formation of **B** [41,68]. Then, reductive elimination from **B** followed by the re-coordination of a PCy_3 ligand would yield the coupling product along with a regeneration of the $\text{Pd}(0)$ species. Another possible route for the coupling reaction might involve the formation of a dimer intermediate $[(\text{PCy}_3)\text{Pd}(\text{C}_6\text{F}_5)(\mu\text{-I})]_2$. Hor argued for the possibility that both catalytic pathways, via mononuclear *cis/trans* geometric isomers and a dinuclear iodide-bridged intermediate, might contribute to the $\text{Pd}(0)$ -catalyzed coupling reaction of pentafluorophenyl iodide with phenylboronic acid [101].

Scheme 14. A plausible reaction mechanism.



3. Conclusions

In this review, we reported recent results for a palladium-catalyzed cross-coupling reaction of perfluoroorganic compounds with organometallic reagents. We have developed the first palladium-catalyzed monoarylation of TFE by employing *in situ*-prepared diarylzinc reagents to yield (α,β,β -trifluoro)styrene derivatives in excellent yield and with high selectivity. C–F bond activation of TFE was achieved by the synergetic effects of the palladium(0) species and LiI to generate the trifluorovinyl palladium(II) intermediate.

We also demonstrated the $\text{Pd}(0)/\text{PR}_3$ -catalyzed cross-coupling reaction of TFE with arylboronate. This reaction required neither an extraneous base to enhance the reactivity of organoboronates nor a Lewis acid additive to promote the oxidative addition of a C–F bond. The key palladium(II) fluoride intermediate that showed a unique reactivity toward organoboron compounds was isolated. These results may open new avenues for the development of a base-free Suzuki-Miyaura coupling reaction including the *in situ* generation of a metal fluoride intermediate via C–F bond activation. Furthermore, our development of palladium-catalyzed selective transformations of TFE via C–F bond activation greatly increases the potential of **1** as a useful starting material for a variety of organofluorine compounds.

In addition, we developed a Pd(0)/PCy₃-catalyzed cross-coupling reaction using C₆F₆ with a variety of diarylzinc compounds to give the corresponding pentafluorobiaryls in good to excellent yields. Stoichiometric reactions employing model complexes, *trans*-(PCy₃)₂Pd(I)(C₆F₅) and *cis*-(C₆F₅)Pd(I)(py)(PCy₃), with diphenylzinc in the presence of lithium iodide revealed both the catalytic reaction mechanism and the role of lithium iodide in this catalytic reaction. The key intermediate in this catalytic cycle was a transient 3-coordinated, monophosphine-ligated species, (PCy₃)Pd(C₆F₅)(I), which was generated by the oxidative addition of the C–F bond of C₆F₆ to Pd(PCy₃)₂ followed by the dissociation of a PCy₃ ligand. In this catalytic reaction, lithium iodide accelerated the oxidative addition step and generated a reactive zincate such as Li[ArZnXI] (*X* = Ar or I) that enabled an efficient transmetalation with the key intermediate. We have also described how this catalytic reaction could be applied to other monocyclic perfluorinated compounds, such as octafluorotoluene and pentafluoropyridine, as well as to polycyclic perfluorinated compounds, such as perfluoronaphthalene and perfluorobiphenyl, to give the corresponding coupling products.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research (A) (No. 21245028), a Grant-in-Aid for Young Scientists (A) (No. 25708018), and a Grant-in-Aid for Scientific Research on Innovative Areas “Molecular Activation Directed toward Straightforward Synthesis” (No. 23105546) from MEXT. Masato Ohashi also acknowledges The Noguchi Institute.

Author Contributions

Masato Ohashi wrote the first draft of the manuscript that was then improved by Sensuke Ogoshi. The literature was researched by both of the authors.

Conflicts of Interest

The authors declare no conflict of interest.

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