### Synthetic Methods

### Palladium-Catalyzed Coupling Reaction of Perfluoroarenes with Diarylzinc Compounds

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**Abstract:** This report describes the first  $Pd^{0}$ -catalyzed crosscoupling of hexafluorobenzene ( $C_{6}F_{6}$ ) with diarylzinc compounds to give a variety of pentafluorophenyl arenes. This reaction could be applied to other perfluoroarenes, such as octafluorotoluene, pentafluoropyridine, and perfluoronaphthalene, to give the corresponding polyfluorinated coupling products. The optimal ligand in this catalytic reaction was PCy<sub>3</sub>, and lithium iodide was indispensable as an additive for the coupling reaction. One of the roles of lithium iodide in this catalytic reaction was to promote the oxidative addition of one C–F bond of  $C_{6}F_{6}$  to palladium. Stoichiometric reactions revealed that an expected oxidative-addition product, *trans*-[Pd( $C_{6}F_{5}$ )I(PCy<sub>3</sub>)<sub>2</sub>], generated from the reaction of [Pd(PCy<sub>3</sub>)<sub>2</sub>] with  $C_{6}F_{6}$  in the presence of lithium iodide, was not involved in the catalytic cycle. Instead, a transient threecoordinate, monophosphine-ligated species,  $[Pd(C_6F_5)]-(PCy_3)]$ , emerged as a potential intermediate in the catalytic cycle. Therefore, we isolated a novel Pd<sup>II</sup> complex,  $[Pd(C_6F_5)]-(PCy_3)(py)]$ , in which pyridine (py) acted as a labile ligand to generate the transient species. In fact, in the presence of lithium iodide, this Pd<sup>II</sup> complex was found to react smoothly with diphenylzinc to give the desired pentafluorophenyl benzene, whereas the same reaction conducted in the absence of lithium iodide resulted in a decreased yield of pentafluorophenyl benzene, which indicated that the other role of lithium iodide was to enhance the reactivity of the organozinc species during the transmetalation step.

#### Introduction

Efficient methods have been developed for the synthesis of organofluorine compounds because functionalized fluorinated organic compounds are indispensable in our daily life. These methods are divided into two major approaches. The first is selective monofluorination at a specific position of an organic compound, which is an essential transformation for the efficient synthesis of pharmaceuticals and agrochemicals. Thus, reactions and reagents for selective fluorination have been developed at a rapid rate.<sup>[1]</sup> The second approach is the selective transformation of a specific carbon-fluorine bond of a perfluoro- or multifluoro-compound, which allows the preparation of organic compounds that include a fluorinated functional group.<sup>[2]</sup> In particular, the transformation of perfluoroarenes is an efficient and economical method for the preparation of highly functionalized organofluorine compounds and, therefore, a limited number of coupling reactions with aryl-metal

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compounds have been reported.<sup>[3-9]</sup> Radius et al. reported the coupling reaction of octafluorotoluene  $(C_7F_8)$  and perfluorobiphenyl ( $C_{12}F_{10}$ ) with aryl boronic acids in the presence of a catalytic amount of NHC-nickel(0) catalyst (NHC = N-heterocyclic carbene).<sup>[3]</sup> This group also demonstrated the usefulness of a NHC-nickel(0) complex for C-F bond activation of hexafluorobenzene ( $C_6F_6$ ); indeed, the Ni<sup>0</sup>/NHC complex showed catalytic activity for the hydro-defluorination of C<sub>6</sub>F<sub>6</sub>.<sup>[10]</sup> However, efficient catalytic transformation of C<sub>6</sub>F<sub>6</sub> in which C-C bond formation is involved is very rare. To the best of our knowledge, only two examples of transition-metal-catalyzed C--C bondforming reactions of C<sub>6</sub>F<sub>6</sub> to give biaryl compounds have been reported to date.<sup>[4,5]</sup> We also demonstrated the reaction of C<sub>6</sub>F<sub>6</sub> with an aryl boronate catalyzed by Radius' complex.<sup>[6]</sup> These reports suggest that nickel catalysts with strong electron-donating ligands are efficient for carbon-fluorine bond activation.<sup>[8, 11, 12]</sup> Yoshikai and Nakamura et al. reported the coupling reaction of multifluorinated benzenes with arylzinc reagents catalyzed by nickel ligated with alkoxydiphosphine; the same group also achieved the selective activation of a C-F bond.<sup>[5]</sup> From a practical point-of-view, however, there is still no easily accessible catalyst system applicable for the coupling reaction that could introduce a perfluorinated aryl group to a specific position of arene compounds. Recently, we reported the palladium-catalyzed coupling reaction of tetrafluoroethylene with diarylzinc reagents to give triflurorovinylarenes, in which lithium iodide was crucial in the oxidative-addition step because of the formation of a very strong Li-F bond.<sup>[13]</sup> This reaction suggested the possibility of cleavage of the unreactive



carbon-fluorine bond of  $C_6F_6$  by the cooperation of palladium(0) and lithium iodide. Herein, we report the coupling reaction of perfluoroarenes (e.g.,  $C_6F_6$ ) with diarylzinc compounds, catalyzed by palladium(0) in the presence of lithium iodide. In addition, this report also introduces a possible reaction pathway for transmetalation with aryl zinc reagents based on certain stoichiometric reactions and the robustness of *trans*-[Pd-( $C_6F_5$ )I(PCy<sub>3</sub>)<sub>2</sub>], formed by the oxidative addition of  $C_6F_6$  to [Pd(PCy<sub>3</sub>)<sub>2</sub>] in the presence of lithium iodide.

#### **Results and Discussion**

### Optimization and substrate scope in the Pd<sup>0</sup>-catalyzed coupling of perfluoroarenes with diarylzinc compounds

We first applied the reaction conditions of the coupling reaction of TFE (tetrafluoroethylene) with  $Ar_2Zn^{[13]}$  to the coupling reaction of  $C_6F_6$  with  $Ar_2Zn$  (Table 1). In the presence of tris(dibenzylideneacetone)dipalladium(0) ([Pd<sub>2</sub>(dba)<sub>3</sub>], 5 mol% (com-

Table 1.	Optimization of the catalyt F F F F F F F F	ric reaction. Pd catalyst additives THF, 60 °C	F F F F F F	∠Ph `F		
Entry	Catalyst ([mol %])	Additive	<i>t</i> [h]	Yield [%] <sup>[a]</sup>		
1	[Pd <sub>2</sub> (dba) <sub>3</sub> ] (5)/PPh <sub>3</sub> (20)	Lil (2.4 equiv)	10	trace		
2	$[Pd(PCy_3)_2]$ (5)	Lil (2.4 equiv)	4	70		
3	none	Lil (2.4 equiv)	21	-		
4	[Pd(PCy <sub>3</sub> ) <sub>2</sub> ] (5)	Lil (3.6 equiv)	6	75		
5	$[Pd(PCy_3)_2]$ (5)	none	10	5		
6 <sup>[b]</sup>	[Pd(OAc) <sub>2</sub> ] (5)/PCy <sub>3</sub> (10)	Lil (2.4 equiv)	4	65		
7	[Pd <sub>2</sub> (dba) <sub>3</sub> ] (5)/PCy <sub>3</sub> (20)	Lil (3.6 equiv)	4	77		
8 <sup>[b]</sup>	[Pd(OAc) <sub>2</sub> ] (5)/DCPE (5)	Lil (2.4 equiv)	9	13		
9 <sup>[b]</sup>	[Pd(OAc) <sub>2</sub> ] (5)/DCPB (5)	Lil (2.4 equiv)	15	trace		
[a] Tetradecane was used as an internal standard. [b] $\rm ZnPh_2$ (0.7 equiv) was employed.						

parable to 10 mol%  $Pd^0$  atom)),  $PPh_3$  (20 mol%), and Lil (2.5 equiv) at 60  $^{\circ}$ C in THF, the reaction of C<sub>6</sub>F<sub>6</sub> with Ph<sub>2</sub>Zn, prepared in situ by treatment of ZnCl<sub>2</sub> with PhMgBr (2 equiv), gave a trace amount of pentafluorophenyl benzene (1) and  $C_6F_6$  remained intact (Table 1, entry 1). To promote the oxidative addition of  $C_6F_6$  to palladium,  $[Pd(PCy_3)_2]$  was examined as a catalyst precursor for the coupling reaction. The desired product 1 was obtained in 70% yield (Table 1, entry 2).<sup>[14,15]</sup> In the absence of a palladium catalyst, no coupling product was observed (Table 1, entry 3). An increase in the amount of Lil improved the yield of 1 to 75% (Table 1, entry 4). In the absence of Lil, 1 was obtained in 5% yield, even after a prolonged reaction time (Table 1, entry 5), which indicates that the addition of Lil is crucial for the occurrence of the coupling reaction. This result contrasted with the reaction of TFE and Ph<sub>2</sub>Zn, generated from PhMgBr and ZnCl<sub>2</sub>, in which 44% of the coupling product was obtained.<sup>[13]</sup> In the presence of PCy<sub>3</sub>, palladium(II) acetate (Pd(OAc)<sub>2</sub>) was also an effective catalyst for the coupling reaction (Table 1, entry 6). A mixture of  $[Pd_2(dba)_3]$  and  $PCy_3$  (5 and 20 mol%, respectively) showed catalytic activity to give **1** in 77% yield, whereas a greater palladium catalyst loading (10 mol%  $[Pd_2(dba)_3]$ ) was required for smooth progress in the coupling reaction (Table 1, entry 7). When either DCPE (1,2-dicyclohexylphosphinoethane) or DCPB (1,4-dicyclohexylphosphinobutane) were employed the coupling reaction was clearly retarded (Table 1, entries 8 and 9).

The palladium-catalyzed coupling reaction of perfluoroarenes with a variety of  $Ar_2Zn$  reagents in the presence of Lil was carried out and the results are summarized in Scheme 1.



**Scheme 1.** Palladium(0)-catalyzed coupling reaction of perfluoroarenes with diarylzinc compounds in the presence of Lil.

Both (4-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>Zn and (3-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>Zn reacted with C<sub>6</sub>F<sub>6</sub> to give coupling products **2** and **3** in 70 and 53% yield, respectively. However, no coupling reaction product was obtained from the reaction of C<sub>6</sub>F<sub>6</sub> with (2-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>Zn. The aryl zinc compounds with electron-donating groups such as (4-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>Zn and (4-MeOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>Zn afforded the coupling compounds **4** and **5** in 74 and 76% yield, respectively. The reac-



tions of aryl zinc reagents with electron-withdrawing groups,  $(4-FC_6H_4)_2Zn$  and  $(3,5-F_2C_6H_3)_2Zn$ , also yielded the corresponding coupling products (**6** and **7**) in 66 and 49% yield, respectively. The reaction of  $C_6F_6$  with  $(2-C_{10}H_9)_2Zn$  under the same reaction conditions gave 2-pentafluorophenylnaphthalene (**8**) in 65% yield after 8 h. When a thienyl group was introduced, the reaction gave 2-pentaphenylthiophene (**9**) in 55% yield. Other functionalized aryl zinc species prepared according to Knochel's procedure,<sup>[16]</sup> LiCl·(*p*-EtCOOC<sub>6</sub>H<sub>4</sub>)Znl and LiCl·(*p*-NCC<sub>6</sub>H<sub>4</sub>)Znl, were successfully applied to the coupling reaction with  $C_6F_6$  to give **10** and **11**, respectively, in moderate isolated yields.

The reaction was applicable to other perfluoroarenes. The coupling reaction of octafluorotoluene  $(C_7F_8)$  with Ph<sub>2</sub>Zn, (4- $MeOC_6H_4)_2Zn$ , or  $(2-MeC_6H_4)_2Zn$  took place at the 4-position of  $C_7F_8$  to give the corresponding products 12–14 in good-to-excellent yields. The reaction of  $C_7F_8$  with  $(4-MeOC_6H_4)_2Zn$  proceeded very smoothly, which allowed the confirmation of a background reaction. In the absence of [Pd(PCy<sub>3</sub>)<sub>2</sub>], 13 was obtained in 30% yield at 60°C for 6 h, which indicates that the palladium-catalyzed coupling reaction proceeds much faster than the background reaction. Perfluoronaphthalene and perfluorobiphenyl reacted with (4-MeOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>Zn to give 2-(4- $MeOC_6H_4)C_{10}F_7$  (15) and 4'-(4-MeOC\_6H\_4)C\_{12}F\_9 (16) in 53 and 32% yield, respectively. In contrast, the reaction of pentafluoropyridine ( $C_5F_5N$ ) with  $Ph_2Zn$  gave a mixture of tetrafluoro-4phenylpyridine (17) and tetrafluoro-2-phenylpyridine (17) in 65 and 17% yield, respectively. Pentafluorobenzene also successfully participated in the coupling reaction with Ph<sub>2</sub>Zn, however, the reaction product was obtained as a mixture of two regioisomers, 2,3,5,6-tetrafluorobiphenyl (18) and 2,3,4,5tetrafluorobiphenyl (18'), and the combined yield of the isomers was only 38%.

## Oxidative addition of perfluoroarenes to $\mathsf{Pd}^0$ in the presence of lithium iodide

To gain deeper insight into the reaction pathway, stoichiometric reactions of C<sub>6</sub>F<sub>6</sub> with palladium(0) complexes were conducted. In a previous report by Grushin et al., the reaction of  $C_6F_6$  with  $[Pd(PCy_3)_2]$  in THF at 70 °C for 24 h occurred very slowly to give a perfluorophenylpalladium(II) fluoride, trans- $[Pd(C_6F_5)F(PCy_3)_2],$  in 3% yield.  $^{[17]}$  On the other hand, in the presence of lithium iodide the oxidative addition proceeded much faster to give a perfluorophenylpalladium(II) iodide, trans- $[Pd(C_6F_5)I(PCy_3)_2]$  (19), which indicates that acceleration of the oxidative addition is an important role of lithium iodide (Scheme 2a). Although the catalytic reaction of  $C_6F_6$  with Ph<sub>2</sub>Zn occurred in the presence of [Pd<sub>2</sub>(dba)<sub>3</sub>] and PCy<sub>3</sub> (4 equiv) to give 1 in 77% yield (Table 1, entry 7), oxidative addition did not occur in the presence of DBA in the stoichiometric reaction at 60°C (Scheme 2b). This result might have been due to inhibition of the coordination of  $C_6F_6$  to palladium by DBA under the stoichiometric reaction conditions and could indicate why [Pd(PCy<sub>3</sub>)<sub>2</sub>] is a more efficient catalyst than the [Pd<sub>2</sub>(dba)<sub>3</sub>]/PCy<sub>3</sub> system. In contrast, even in the presence of lithium iodide, the oxidative addition of  $C_6F_6$  to  $[Pd(PPh_3)_4]$  did



Scheme 2. Stoichiometric reaction of  $\mathsf{C_6F_6}$  with  $\mathsf{Pd^0/PCy_3}$  in the presence of Lil.

not take place, which is consistent with the observation that no reaction occurred in the presence of PPh<sub>3</sub> (Table 1, entry 1).

The ORTEP representation of **19** unambiguously demonstrates that the palladium center in **19** adopts a square-planar coordination geometry and is coordinated by two PCy<sub>3</sub> ligands in a *trans* manner (Figure 1). A similar coordination geometry was observed in structurally well-defined Pd<sup>II</sup> complexes, such as *trans*-[Pd(C<sub>6</sub>F<sub>5</sub>)Cl(PPh<sub>3</sub>)<sub>2</sub>] and *trans*-[Pd(C<sub>6</sub>F<sub>5</sub>)I(PCy<sub>2</sub>Fc)<sub>2</sub>] (Fc = ferrocenyl).<sup>[18]</sup>



**Figure 1.** ORTEP drawing of **19** with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity.

Similar oxidative-addition products, *trans*-[Pd(*p*-CF<sub>3</sub>C<sub>6</sub>F<sub>4</sub>)l-(PCy<sub>3</sub>)<sub>2</sub>] (**20**) and *trans*-[Pd(2-C<sub>10</sub>F<sub>7</sub>)l(PCy<sub>3</sub>)<sub>2</sub>] (**21**), can be isolated by treatment of either C<sub>7</sub>F<sub>8</sub> or perfluoronaphthalene with [Pd(PCy<sub>3</sub>)<sub>2</sub>] in the presence of lithium iodide (Scheme 3). In the former reaction, the C–F bond at the 4-position of perfluoroto-luene was exclusively cleaved, whereas the C–F bond at the 2-position of perfluoronaphthalene was exclusively activated in the latter reaction. These regioselectivities of C–F bond activation were consistent with those observed in the corresponding catalytic reaction (Scheme 1), as well as with those observed in the reactivity of [{(NHC)<sub>2</sub>Ni<sub>2</sub>(cod)] (cod = 1,5-cyclooctadiene).<sup>[3,10b]</sup> The ORTEP drawings of **20** and **21** are represented in Figure 2, and definitely show that the palladium center in both **20** and **21** has the same coordination geometry as in **19**.



Scheme 3. Stoichiometric reaction of either  $C_7F_8$  or  $C_{10}F_8$  with  $[Pd(PCy_3)_2]$  in the presence of Lil.



**Figure 2.** ORTEP drawings of **20** (top) and **21** (bottom) with thermal ellipsoids at the 30% probability level. One of the two independent molecules in a unit cell of **20** is depicted. Hydrogen atoms and solvate molecules (hexane) are omitted for clarity.

# Reactivity of 20 toward $Ph_2Zn$ and preparation of $[Pd(C_6F_5)I-(PCy_3)(py)]$ (22)

To confirm whether or not **19** is an intermediate in the  $Pd^{0}$ -catalyzed cross-coupling reaction of  $C_6F_6$  with diarylzinc compounds, a stoichiometric reaction of **19** with diphenylzinc was carried out. A yield of only 5% of **1** was obtained from a stoi-



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Scheme 4. Reaction of 19 with diphenylzinc in the presence of Lil.

chiometric reaction conducted at 60°C for 7 h in the presence of an excess amount of lithium iodide (Scheme 4), whereas 1 was obtained in 69% yield under the catalytic reaction conditions mentioned above (60 °C, 6 h; Scheme 1). This result strongly indicates that 19 is unlikely to be a reaction intermediate due to the steric hindrance around the palladium center caused by the two bulky PCy<sub>3</sub> ligands. Thus, we assumed that oxidative addition of  $C_6F_6$  to  $[Pd(PCy_3)_2]$  in the presence of lithium iodide might involve dissociation of a PCy<sub>3</sub> ligand to give a transient  $[Pd(C_6F_5)I(PCy_3)]$  species. The resultant three-coordinate transient intermediate would undergo re-coordination of a PCy<sub>3</sub> ligand in the absence of ZnPh<sub>2</sub> to yield the thermodynamically favored, and unreactive, species 19. On the other hand, in the presence of ZnPh<sub>2</sub>, transmetalation between the transient iodopalladium(II) species and ZnPh<sub>2</sub> would take place smoothly to give the coupling product 1. These assumptions are consistent with the results from kinetic studies performed by Hartwig and co-workers: the oxidative addition of chlorobenzene to [Pd(PCy<sub>3</sub>)<sub>2</sub>], to give trans-[PdCl- $(PCy_3)_2(Ph)$ ] involved the dissociation of a PCy<sub>3</sub> ligand at the initial stage of the reaction.<sup>[19]</sup> Unfortunately, any attempt to prepare the transient intermediate failed due to its coordinative unsaturation and, therefore,  $[Pd(C_6F_5)I(PCy_3)(py)]$  (22), in which pyridine acts as a labile ligand to generate a tentative threecoordinate  $[Pd(C_6F_5)I(PCy_3)]$  species, was prepared as an alternative catalytic precursor.

A synthetic route for preparation of **22** is summarized in Scheme 5. We chose  $[Pd(C_6F_5)_2(py)_2]$  (**23**)<sup>[20]</sup> as a starting material. In accordance with the literature,<sup>[21]</sup> treatment of  $[PdCl_2(py)_2]$  with  $C_6F_5Li$  (3 equiv), generated in situ by reaction of  $C_6F_5Cl$  with *n*BuLi at -78 °C, gave **23** in 72 % yield. The reaction of **23** with PdCl<sub>2</sub> in acetone,<sup>[22]</sup> followed by treatment with PCy<sub>3</sub> in





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pyridine, resulted in the formation of  $[Pd(C_6F_5)Cl(PCy_3)(py)]$  (24) in 32% yield. Substitution of an iodide for the chloride ligand in 24 was accomplished by treatment of a solution of 24 in acetone with excess Nal to afford the desired palladium(II) iodide 22 in 55% yield.

In the <sup>19</sup>F NMR spectrum of the bis(pentafluorophenyl)palladium complex **23**, three resonances assigned to the *ortho-*, *meta-*, and *para-*positions of the pentafluorophenyl rings appeared with an integral ratio of 2:2:1, and the combustion analysis of **23** agreed with the original literature. However, an X-ray diffraction study of **23** revealed that the Pd<sup>II</sup> center had a square-planar geometry and was coordinated by two pentafluorophenyl ligands in the *cis* configuration, although a *trans* configuration was proposed in the original literature (Figure 3).<sup>[20]</sup> This result clearly demonstrates that, at least in



Figure 3. ORTEP drawing of 23 with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity.

the crystal lattice, **23** is the *cis* isomer. Both the pyridine and pentafluorophenyl rings in **23** were tilted away from the palladium coordination plane to reduce the steric repulsion (dihedral angles=81.91(9) and  $66.37(8)^{\circ}$  for the pyridine rings; 78.61(9) and  $68.93(8)^{\circ}$  for the pentafluorophenyl rings).

The novel pentafluorophenyl palladium(II) halides 22 and 24 were characterized by NMR spectroscopy and elemental analysis, as well as by X-ray diffraction analysis. The <sup>1</sup>H NMR spectra of these complexes clearly showed that both the pyridine and PCy<sub>3</sub> ligands were coordinated to the Pd<sup>II</sup> center in a ratio of 1:1. In addition, the ligands in 22 and 24 were situated in a mutual *cis* position with a square-planar Pd<sup>II</sup> geometry, as shown by X-ray diffraction (Figure 4). The Pd-N bond lengths of 2.032(10) Å in 22 and 2.0407(13) Å in 24 were slightly shorter than those observed in 23 (2.093(2) and 2.105(3) Å), which reflects the difference in the trans influence between halides and a pentafluorophenyl ligand. In contrast, the Pd–C<sub>6</sub>F<sub>5</sub> bond lengths showed no significant differences (2.015(5) Å for 19, 2.069(12) Å for 22, 2.001(3) and 2.025(3) Å for 23, and 2.0519(16) Å for 24). In addition, the bond lengths between the palladium and phosphorus atoms in 22 and 24 (2.359(3) and 2.3604(4) Å, respectively) were close in value to those observed in 19 (2.3691(16) and 2.3839(16) Å).





**Figure 4.** ORTEP drawings of **24** (top) and **22** (bottom) with thermal ellipsoids at the 30% probability level. Hydrogen atoms and solvate molecules (THF) in **22** are omitted for clarity.

#### Reactivity of 22 toward diphenylzinc

We next evaluated the reactivity of **22** toward diphenylzinc in the presence or absence of lithium iodide; the results are summarized in Scheme 6. In the presence of lithium iodide



Scheme 6. Reactions of 22 with ZnPh<sub>2</sub> in the presence or absence of Lil.

(1.5 equiv), **22** reacted smoothly with  $ZnPh_2$ , which was carefully purified by sublimation prior to use, in THF at room temperature to give the desired coupling product **1** as the sole product in 63% yield. The addition of PCy<sub>3</sub> to this reaction mixture affected neither the yield nor the selectivity of the reaction product. On the other hand, in the absence of lithium iodide, the reaction of **22** with  $ZnPh_2$  under the same reaction conditions afforded a pentafluorophenylzinc species,  $C_6F_5ZnX$  (X = I or  $C_6F_5$ ), as the major product (54%) and **1** as the minor prod-

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uct (27 %). These observations suggest the following: 1) a transient  $[Pd(C_6F_5)I(PCy_3)]$  species, generated by dissociation of the labile pyridine ligand of **22**, could be crucial for the smooth occurrence of transmetalation between the palladium(II) species and ZnPh<sub>2</sub>, and 2) the existence of lithium iodide is essential for selective transmetalation to generate **1**.

Based on these results, a plausible reaction mechanism was proposed (Scheme 7). In the presence of lithium iodide, oxidative addition of a C–F bond in  $C_6F_6$  to  $Pd^0$  would occur by dis-



Scheme 7. A plausible mechanism.

sociation of a PCy<sub>3</sub> ligand to form a  $[Pd(C_6F_5)I(PCy_3)]$  intermediate (A). We assume that the Lil-promoted C-F bond activation of  $C_6F_6$  on  $[Pd(PCy_3)_2]$  would take place to give the *cis*-oxidative-addition product, then the rapid dissociation of a PCy<sub>3</sub> ligand might occur due to the steric hindrance of the two bulky phosphine ligands. On the basis of theoretical and experimental studies, Radius et al. assumed that a related C-F bond activation of C<sub>6</sub>F<sub>6</sub> on a Ni(NHC)<sub>2</sub> fragment, to yield trans- $[Ni(NHC)_2(C_6F_5)F]$ , would proceed by the corresponding *cis*-oxidative-addition product.<sup>[10b]</sup> Transmetalation between A and the diarylzinc compound in the presence of lithium iodide would take place to give a bisarylpalladium(II) intermediate (B). This transmetalation step would progress in preference to the re-coordination of a PCy3 ligand to give unreactive trans-[Pd- $(C_6F_5)I(PCy_3)_2]$  (A'). The role of lithium iodide in this reaction step might be rationalized by the formation of a reactive zincate, such as Li[ArZnXI] (X = Ar or I), which would enable the efficient formation of **B**.<sup>[13,23]</sup> Then, reductive elimination from **B**, followed by the re-coordination of a PCy<sub>3</sub> ligand would yield the coupling product, along with regeneration of the Pd<sup>0</sup> species.

Another possible route for the coupling reaction might involve the formation of a dimer intermediate,  $[Pd(C_6F_5)(\mu-I)(PCy_3)]_2$ . Hor et al. argued for the possibility that both catalytic pathways, via mononuclear *cis/trans* geometric isomers and via a dinuclear iodide-bridged intermediate, may contribute to the Pd<sup>0</sup>-catalyzed coupling reaction of pentafluorophenyl iodide with phenylboronic acid.<sup>[18b]</sup>

#### Conclusion

We have demonstrated the Pd<sup>0</sup>/PCy<sub>3</sub>-catalyzed cross-coupling reaction of  $C_6F_6$  with a variety of diarylzinc compounds to give the corresponding pentafluorobiaryl compounds in good-toexcellent yields. Stoichiometric reactions that employed model complexes, trans- $[Pd(C_6F_5)I(PCy_3)_2]$  and  $[Pd(C_6F_5)I(PCy_3)(py)]$ , 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 is a transient, three-coordinated, monophosphine-ligated species, [Pd(C<sub>6</sub>F<sub>5</sub>)I(PCy<sub>3</sub>)], which was generated by oxidative addition of the C–F bond of  $C_6F_6$  to  $[Pd(PCy_3)_2]$ , followed by dissociation of a PCy<sub>3</sub> ligand. The role of lithium iodide in this catalytic reaction was not only to accelerate the oxidative addition step, but also to generate a reactive zincate, such as Li[ArZnXI] (X = Ar or I), which would enable an efficient transmetalation with the key intermediate. We have also demonstrated that 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.

#### **Experimental Section**

#### General

All manipulations were conducted under a nitrogen atmosphere by using standard Schlenk or drybox techniques. <sup>1</sup>H, <sup>19</sup>F, <sup>31</sup>P, and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance III 400 spectrometer. The chemical shifts in the <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded relative to residual protic solvent. The chemical shifts in the <sup>31</sup>P NMR spectra were recorded by using aqueous H<sub>3</sub>PO<sub>4</sub> (85%) as an external standard. The chemical shifts in the <sup>19</sup>F NMR spectra were recorded relative to  $\alpha, \alpha, \alpha$ -trifluorotoluene ( $\delta = -62.8$  ppm in CDCl<sub>3</sub>). Recycling preparative HPLC was performed with a Japan Analytical Industry LC9225NEXT instrument equipped with JAIGEL-1H and JAIGEL-2H in-line columns. Elemental analyses were performed at the Instrumental Analysis Center, Faculty of Engineering, Osaka University. X-ray crystal data were collected with a Rigaku RAXIS-RAPID Imaging Plate diffractometer or Mercury 375R/M CCD (XtaL LAB mini) diffractometer.

#### Materials

The degassed and distilled solvents (toluene and hexane) used in this work were commercially available. THF,  $[D_8]$ THF, and  $C_6D_6$  were distilled from sodium benzophenone ketyl. All the Grignard reagents used in this work were purchased from Aldrich as THF solutions and their concentrations were determined by titration with a solution of *sec*-BuOH in absolute *m*-xylene in the presence of 1,10-phenanthroline as an indicator. *Trans*-bis-(pyridine)dichloropalladium(II),<sup>[21]</sup> [Pd(PCy<sub>3</sub>)<sub>2</sub>],<sup>[24]</sup> a solution of LiCl-(*p*-cyanophenyl)zinc iodide in THF,<sup>[16]</sup> and LiCl-(*p*-EtCOOPh)zinc iodide<sup>[16]</sup> were prepared by published procedures. Zinc chloride (3N) was purchased from WAKO Pure Chemicals, and dried under vacuum with heating until melting. Other commercially available reagents were distilled and degassed prior to use.



#### General procedure for the optimization of the catalytic reaction

In a drybox, ZnCl<sub>2</sub> (9.54 mg, 0.07 mmol), PhMgBr (1  $\mbox{m}$  in THF, 140  $\mbox{m}$ L, 0.14 mmol), Lil (32.1 mg, 0.24 mmol), and THF (160  $\mbox{m}$ L) were added to a vial equipped with a stirrer bar. A solution of Pd(OAc)<sub>2</sub> (1.1 mg, 0.005 mmol) in THF, PCy<sub>3</sub> (2.8 mg, 0.010 mmol), 1 (11.5  $\mbox{m}$ L, 0.1 mmol), and tetradecane (26  $\mbox{m}$ L, 0.1 mmol), as an internal standard, were added to the mixture. The vial was sealed and heated, with stirring, by means of a preheated sand bath. After the reaction was complete, the solution was quenched with methanol and analyzed by GC. The yield was estimated by comparison of the peak areas of pentafluorobiphenyl and tetradecane with a sensitivity ratio determined by the GC spectra of isolated samples.

#### General procedure for the Pd<sup>0</sup>-catalyzed coupling of perfluoroarenes with diarylzinc compounds in the presence of Lil

In a drybox, a solution of aryImagnesium halide (1.2 mmol) in THF and ZnCl<sub>2</sub> (81.8 mg, 0.6 mmol) were added to a vial equipped with a stirrer bar. The mixture was diluted with THF (total volume = 5 mL) and vigorously stirred until ZnCl<sub>2</sub> dissolved completely. [Pd(PCy<sub>3</sub>)<sub>2</sub>] (33.3 mg, 0.05 mmol), Lil (321 mg, 2.4 mmol), and perfluroarene (0.1 mmol) were added to the solution. The reaction mixture was heated with stirring, then quenched with an aqueous solution of 1 mmole HCl (15 mL). The water layer was separated and extracted with ether (4×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and evaporated to dryness. The resulting solid was purified by flash column chromatography to give pure product.

#### Isolation of compound 19

In a drybox, [Pd(PCy<sub>3</sub>)<sub>2</sub>] (202 mg, 0.3 mmol), Lil (41 mg, 0.3 mmol),  $C_6F_6$  (34.5  $\mu$ L, 0.3 mmol), and THF (5 mL) were added. The reaction mixture was stirred at 60 °C for 5 h in a metal bath. Volatile compounds were removed under vacuum and the resultant solid was extracted with Et<sub>2</sub>O, filtered, and dried under vacuum to afford 19 as a yellow solid (197 mg, 68%). Recrystallization from Et<sub>2</sub>O at -35°C afforded good crystals for analysis by X-ray diffraction. <sup>1</sup>H NMR (400 MHz,  $C_6D_6$ , rt):  $\delta = 2.4-1.0$  ppm (m, 66 H; Cy group); <sup>19</sup>F NMR (376 MHz, C<sub>6</sub>D<sub>6</sub>, rt):  $\delta = -111.2$  (d, J = 27.4 Hz, 2F), -164.7(t, J=20.1 Hz, 1F), -166.0 ppm (m, 2F); <sup>31</sup>P NMR (162 MHz, C<sub>6</sub>D<sub>6</sub>, rt):  $\delta = 29.3$  ppm (s); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>, rt):  $\delta = 37.1$  (t, J= 9.7 Hz), 30.8, 28.0 (t, J=5.2 Hz), 26.7 ppm (signals assigned to the  $C_6 F_5$  moiety could not be detected due to multiple  $^{13}\text{C}{-}^{19}\text{F}$  couplings); elemental analysis calcd (%) for  $C_{42}H_{66}F_5IP_2Pd$ : C 52.48, H 6.92; found: C 52.45, H 7.10; X-ray data for 19: M,=961.19; colorless; monoclinic;  $P2_1/c$  (no. 14); a = 16.474(11), b = 16.227(10), c =17.847(12) Å;  $\beta = 116.358(6)^{\circ}$ ; V = 4275(5) Å<sup>3</sup>; Z = 4;  $ho_{
m calcd} =$ 1.493 g cm<sup>-3</sup>; T = -120(0) °C;  $R_1$  ( $wR_2$ ) = 0.0551 (0.1086).

#### Preparation of compound 23<sup>[20]</sup>

Absolute ether (20 mL, dried over sodium benzophenone ketyl) and chloropentafluorobenzene (740  $\mu$ L, 6.0 mmol) were added to a two-necked round-bottomed flask equipped with a stirrer bar. The solution was cooled to -78 °C. A solution of *n*BuLi (1.6 M, 3.8 mL, 6.0 mmol) in hexane was added dropwise with stirring (*Caution!* (Pentafluorophenyl)lithium is very thermally unstable and to avoid explosion it must be prepared and reacted at low temperatures). The colorless solution was stirred for 30 min at

-78 °C. Then, [PdCl<sub>2</sub>(py)<sub>2</sub>] (670 mg, 2.0 mmol) was added to the solution. The resultant yellow suspension was stirred at  $-78\,^\circ\text{C}$  for 1 h, then warmed to rt and stirred for 2 h. The resulting white suspension was quenched with ether (5 mL) that contained a small amount of water and evaporated to dryness. The residue was extracted with boiling acetone and the acetone solution was filtered through a pad of Celite and dried out. Recrystallization from hot acetone/ethanol at -30°C overnight afforded 23 as white needles (862 mg, 72%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, rt):  $\delta = 8.74$  (m, 4H), 7.64 (tt, J=7.8, 1.5 Hz, 2 H), 7.23 ppm (m, 4 H); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, rt):  $\delta = -122.4$  (m, 4F), -160.4 (t, J = 19.5 Hz, 2F), -162.5 ppm (m, 4F);  $^{\rm 13}{\rm C}$  NMR (100 MHz, CDCl<sub>3</sub>, rt):  $\delta\!=\!$  153.4, 137.8, 125.4 ppm (signals assigned to the  $C_6F_5$  moiety could not be detected due to multiple <sup>13</sup>C-<sup>19</sup>F couplings), elemental analysis calcd (%) for C<sub>22</sub>H<sub>10</sub>F<sub>10</sub>N<sub>2</sub>Pd: C 44.13, H 1.68, N 4.68; found: C 44.11, H 1.89, N 4.74; X-ray data for 23:  $M_r = 598.72$ ; colorless; monoclinic;  $P2_1/$ c (no. 14); a = 9.8891(10), b = 16.9318(13), c = 13.0111(12) Å;  $\beta =$ 109.524(3)°; V=2053.3(3) ų; Z=4;  $ho_{\rm calcd}$ =1.937 g cm<sup>-3</sup>; T= -150(0) °C;  $R_1$  ( $wR_2$ ) = 0.0355 (0.0786).

#### Preparation of [Pd(C<sub>6</sub>F<sub>5</sub>)Cl(py)<sub>2</sub>]<sup>[22]</sup>

Compound 23 (599 mg, 1.0 mmol), PdCl<sub>2</sub> (195 mg, 1.1 mmol), and acetone (35 mL) were added to a round-bottomed flask equipped with a stirrer bar. The resultant reddish-brown suspension was heated at reflux for 3 h with vigorous stirring. After the reddishbrown suspension of PdCl<sub>2</sub> disappeared, pyridine (1 mL) was added. After an additional 30 min of heating at reflux, the volatile compounds were removed by evaporation. The resulting solid was extracted with Et<sub>2</sub>O. The organic layer was evaporated to dryness and recrystallization from acetone afforded  $[Pd(C_6F_5)Cl(py)_2]$  as white needles (541 mg, 58%). <sup>1</sup>H NMR (400 MHz,  $C_6D_{67}$  rt):  $\delta = 8.60$ (m, 4H), 6.44 (tt, J=7.8, 1.5 Hz, 2H), 6.13 ppm (m, 4H); <sup>19</sup>F NMR (376 MHz,  $C_6D_{6r}$  rt):  $\delta = -125.1$  (m, 2F), -162.0 (t, J = 20.2 Hz, 1F), -164.9 ppm (m, 2F); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>, rt):  $\delta = 153.4$ , 137.6, 124.7 ppm (signals assigned to the  $C_6F_5$  moiety could not be detected due to multiple <sup>13</sup>C-<sup>19</sup>F couplings); elemental analysis calcd (%) for  $C_{16}H_{10}CIF_5N_2Pd$ : C 41.14, H 2.16, N 6.00; found: C 41.29, H 2.38, N 6.09. In the <sup>1</sup>H and <sup>13</sup>C NMR spectra, the two pyridine rings were observed equivalently, which indicated they occupy the trans positions of the square-planar Pd<sup>II</sup> geometry. The configuration of the product, however, was not mentioned in the original literature.<sup>[22]</sup>

#### Preparation of compound 24

In a dry box, PCy<sub>3</sub> (287 mg, 1.02 mmol) was added to a solution of  $[Pd(C_6F_5)Cl(py)_2]$  (434 mg, 0.93 mmol) in pyridine (7 mL). Hexane was added to the resultant yellow solution to give a yellowishwhite precipitate. The suspension was filtered and washed with hexane to give a yellowish-white powder. The crude material was recrystallized from acetone by cooling to -35 °C to yield yellow block crystals of 24-acetone (320 mg, 52%). <sup>1</sup>H NMR (400 MHz,  $[D_8]$ THF, rt):  $\delta = 8.88$  (m, 2 H), 7.85 (tt, J=7.6, 1.5 Hz, 1 H), 7.45 (m, 2H), 2.1–1.0 ppm (m, 33H; Cy group); <sup>19</sup>F NMR (376 MHz, [D<sub>8</sub>]THF, rt):  $\delta = -127.5$  (m, 2 F), -169.3 (t, J = 19.6 Hz, 1 F), -170.5 ppm (m, 2F); <sup>31</sup>P NMR (162 MHz, [D<sub>8</sub>]THF, rt):  $\delta = 17.7$  ppm (m); <sup>13</sup>C NMR (100 MHz, [D<sub>8</sub>]THF, rt):  $\delta$  = 154.5, 139.2, 126.8, 33.6 (d, J(C,P) = 17 Hz), 30.4, 28.3 (d, J(C,P) = 11 Hz), 27.0 ppm (signals assigned to the  $C_6F_5$  moiety could not be detected due to multiple  ${}^{13}C-{}^{19}F$  couplings); elemental analysis calcd (%) for C<sub>29</sub>H<sub>38</sub>ClF<sub>5</sub>NPPd·C<sub>3</sub>H<sub>6</sub>O: C 52.90, H 6.10, N 1.93; found: C 53.03, H 6.29, N 2.09; X-ray data for **24**-acetone:  $M_r = 726.50$ ; yellow; monoclinic;  $P2_1/c$  (no. 14); a =9.8563(4), b = 16.1075(7), c = 20.7981(10) Å;  $\beta = 100.527(2)^{\circ}$ ; V =

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3246.3(3) Å<sup>3</sup>; Z=4;  $\rho_{calcd}$ =1.486 g cm<sup>-3</sup>; T=-120(0) °C; R<sub>1</sub> (wR<sub>2</sub>)= 0.0241 (0.0281).

#### Preparation of compound 22

In a drybox, Nal (300 mg, 2.0 mmol) was added to a solution of 24 (145 mg, 0.2 mmol) in acetone (10 mL). The resultant orange solution was stirred for 3 h. The solution turned to an orange suspension. Toluene (30 mL) was added and the resultant precipitates were removed by filtration. All volatile compounds were removed under vacuum and the resultant solid was taken out of the drybox. The solid was washed with ethanol until no yellow color was observed in the wash liquor, then washed with small amount of water and ethanol. The resultant solid was dissolved in acetone and dried under vacuum to give 22 as a yellow powder (83 mg, 55%). The complex was recrystallized from THF/hexane. <sup>1</sup>H NMR (400 MHz, [D<sub>6</sub>]acetone, rt):  $\delta = 8.86$  (d, J = 5.2 Hz, 2 H), 7.98 (tt, J =7.6, 1.5 Hz, 1 H), 7.62 (m, 2 H), 2.1-1.0 ppm (m, 33 H; Cy group);  $^{19}\text{F}$  NMR (376 MHz, [D\_6]acetone, rt):  $\delta\!=\!-123.2$  (m, 2F), -167.3 (t, J=18.6 Hz, 1F), -168.7 ppm (m, 2F); <sup>31</sup>P NMR (162 MHz,  $[D_6]$ acetone, rt):  $\delta = 21.0$  ppm (m); <sup>13</sup>C NMR (100 MHz,  $[D_6]$ acetone, rt):  $\delta = 154.0$ , 140.0, 127.5, 35.1 (d, J(C,P) = 18 Hz), 31.1, 28.5 (d, J(C,P) = 10 Hz), 27.1 ppm (signals assigned to the C<sub>6</sub>F<sub>5</sub> moiety could not be detected due to multiple  ${}^{13}C-{}^{19}F$  couplings); elemental analysis calcd (%) for  $C_{29}H_{38}F_5INPPd\colon C$  45.84, H 5.04, N 1.84; found: C 45.92, H 5.65, N 2.39; X-ray data for 22-C<sub>4</sub>H<sub>8</sub>O: M<sub>r</sub>=831.98; colorless; monoclinic;  $P2_1/n$  (no. 14); a=9.9348(4), b=16.3295(7), c=21.2257(9) Å;  $\beta = 105.0560(10)^{\circ}$ ; V = 3325.2(2) Å<sup>3</sup>; Z = 4;  $\rho_{calcd} =$ 1.646 g cm<sup>-3</sup>; T = -150(0) °C;  $R_1$  ( $wR_2$ ) = 0.1348 (0.3479).

CCDC-958538 (**19**), -958539 (**20**·C<sub>6</sub>H<sub>14</sub>), -958540 (**21**·0.5(C<sub>6</sub>H<sub>14</sub>)), -958541 (**22**·C<sub>4</sub>H<sub>8</sub>O), -958542 (**23**), and -958543 (**24**·C<sub>3</sub>H<sub>6</sub>O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.

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