Palladium-Catalyzed Direct Arylation of Polyfluoroarenes for Accessing Tetra-*ortho*-Substituted Biaryls: Buchwald-type Ligand Having Complementary –PPh_2 Moiety Exhibits Better Efficiency

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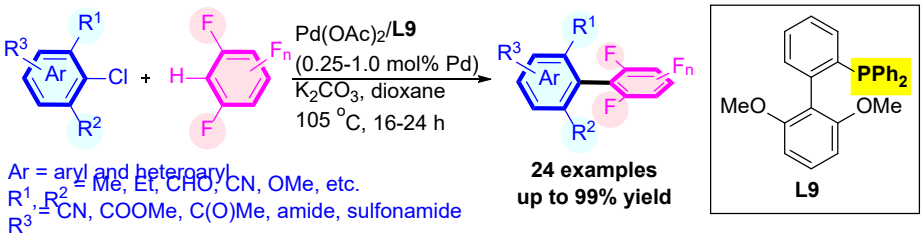


ABSTRACT. The first general examples of direct C-H arylation of electron-deficient polyfluoroarenes with challenging di-*ortho*-substituted aryl(heteroaryl) chlorides for tetra-*ortho*-substituted biaryl

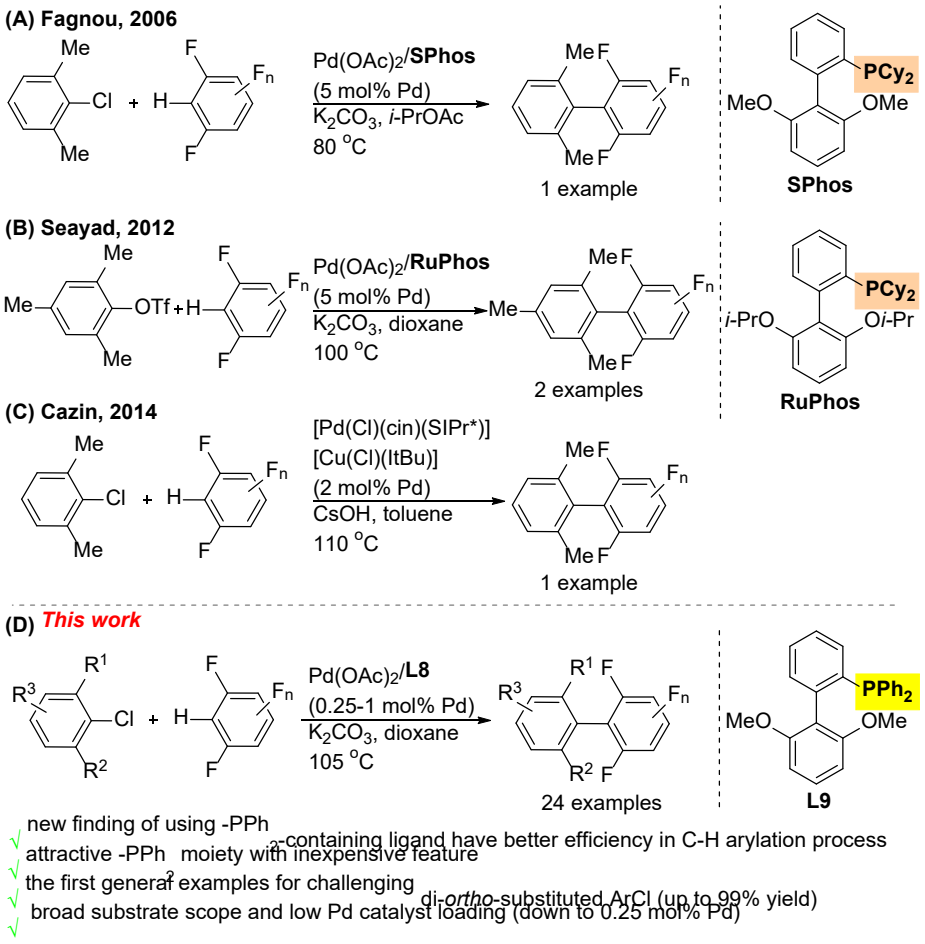
synthesis is reported. Key to success is the use of Buchwald-type biaryl phosphine ligand, notably with inexpensive $–PPh_2$ moiety (instead of $–PCy_2$ group). $Pd(OAc)_2$ associated with ligand **L9** exhibits even higher efficiency than the corresponding SPhos towards this reaction. A wide range of sterically hindered di-*ortho*-substituted chloroarenes bearing electron-donating or -withdrawing groups are found applicable. Excellent product yields are obtained under mild reaction conditions and the catalyst loading down to 0.25 mol% of Pd can also be achieved.

Introduction

Palladium-catalyzed cross-coupling reactions are versatile protocols for the connection of two different organic fragments together *via* the formation of carbon-carbon and/or carbon-heteroatom bonds.[1] Suzuki-Miyaura,[2] Negishi,[3] Kumada,[4] Stille[5] and Hiyama[6] reactions are widely adopted methods for the construction of useful biaryls. Although they are relatively mature technologies, some non-circumvented factors still exist. Likewise, the organometallic nucleophiles may need to be prepared prior to use or may not be straightforwardly available. Moreover, subsequent disposal of the stoichiometric amount of organometallic waste is also a concern. In fact, direct C–H arylation is an attractive alternative for accessing biaryl compounds, and allows a better atom (and step) economy and ultimately streamlines the chemical synthesis.[7,8]

Polyfluorobiaryl motifs are often found in biologically active compounds, pharmaceutically useful molecules, natural products, and functional materials.[9] Employing polyfluoroarenes directly as the substrate is a more desirable synthetic choice than their corresponding organometallic reagents. For instance, the highly electron-deficient polyfluoroaryl organometallic nucleophiles (e.g. $C_6F_5B(OH)_2$) constitute a challenging substrate class because their preparation is difficult and not straightforward.[10] They often undergo a slow transmetallation process in the catalytic cycle. Moreover, electron-deficient arylboronic acids are moderately stable and usually decompose *via* rapid protodeboronation in the aqueous base during the course of the reactions.[10,11]

Although remarkable progress has been made in palladium-catalyzed direct C–H arylation of polyfluoroarenes with aryl halides and sulfonates,[12] a general catalyst system allowing the challenging sterically hindered aryl halides, in particular aryl chlorides, in the synthesis of tetra-*ortho*-substituted polyfluorobiaryl remained limited. Daugulis showed steric congested aryl iodide which was well-couple with perfluoroarenes.[13] In 2006, Fagnou reported one example of sterically congested di-*ortho*-substituted aryl chloride in the direct arylation of perfluoroarene (Scheme 1A).[14] A 5 mol% $Pd(OAc)_2$ with electron-rich SPhos ligand was used as the catalyst system. In 2012, Seayad employed $Pd(OAc)_2$ and RuPhos to promote the direct C–H arylation of polyfluoroarenes with sterically hindered aryl triflates (Scheme 1B).[15] Two examples of di-*ortho*-substituted aryl triflates were shown, under the condition of 5 mol% Pd catalyst loading. Recently, Cazin developed a new Pd-NHC/Cu-NHC cooperative system to facilitate this cross-coupling reaction (Scheme 1C),[16] in affording moderate product yield (41%).

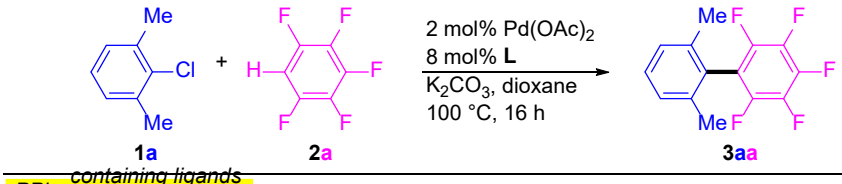


Scheme 1. Direct Arylation of Polyfluoroarenes with Sterically Hindered Aryl Chlorides or Sulfonates

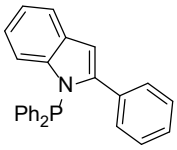
Monophosphine ligand bearing sterically bulky dialkylphosphino group (where alkyl = Cy, *t*-Bu, Ad, *i*-Pr) is believed to be a crucial parameter for overcoming the challenging cross-coupling reactions, due to its favorable electronic and steric characters facilitate the oxidative addition and reductive elimination steps, respectively, in the catalytic cycle.[17] While Ar-PR_2 ligands are often employed in various coupling processes nowadays, the less electron-rich and less steric bulky Ar-PPh_2 ligands receive not as much of attention. In fact, the electronic and steric factors of the ligand always interplay with the efficiency of oxidative addition and reductive elimination processes. Therefore, an on contrary hypothetical view is that too proximal-bulky ligand may not allow substrate approaching effectively for oxidative addition, and too electron-rich ligand may not much electronically favor reductive elimination. There has been shortcoming in direct C-H arylation of polyfluoroarenes using sterically hindered aryl chlorides. Indeed, it is highly desirable to tackle this problem using a tailor-made ligand approach. Herein, we report a new catalyst system for general direct arylation of polyfluoroarene for difficult tetra-*ortho*-substituted biaryl synthesis. Key to success of this sterically congested reaction is the balance of the electronic and steric factors of the monophosphine ligand. Particularly noteworthy is that the –PPh_2-

containing ligand even exhibited better efficacy than the corresponding –PCy_2-containing SPhos.[18]

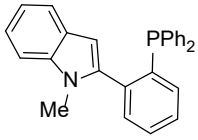
Results and Discussion



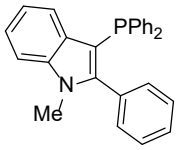
-PPh_2 containing ligands



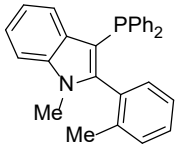
L1
trace



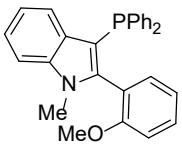
CM-Phos
40%



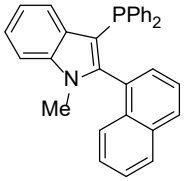
L2
36%



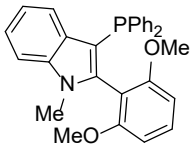
L3
82%



L4
89%

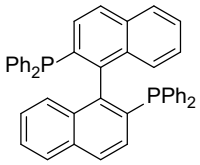


L5
98% (2.00 mol% Pd)
79% (0.25 mol% Pd)
78% (0.25 mol% Pd)[b]

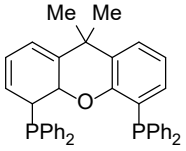


L6
77%

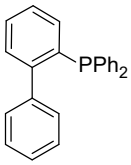
Ph_3P, 1%
dppm, trace
dppe, trace
dppp, 1%
dppf, trace



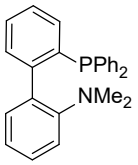
BINAP
trace



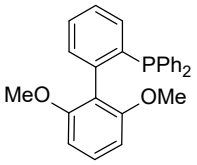
XantPhos
trace



L7
2%



L8
11%



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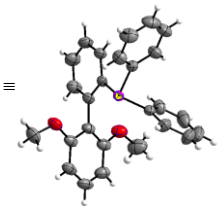
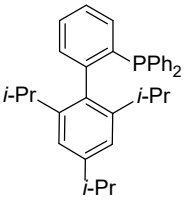
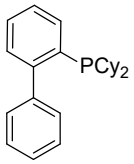




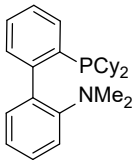
L9
99% (2.00 mol% Pd)
80% (0.25 mol% Pd)
99% (0.25 mol% Pd)[b]

L10
82%

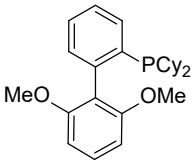
-PCy_2 containing ligands



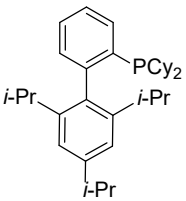
CyJohnPhos
trace



DavePhos
4%



SPhos
96% (2.00 mol% Pd)
41% (0.25 mol% Pd)

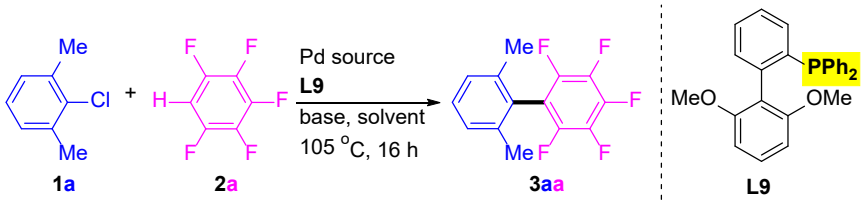


XPhos
71%

Scheme 2. An Evaluation of Ligand Efficacy[a] ([a]Reaction conditions: 2-Chloro-1,3-dimethylbenzene (0.5 mmol), pentafluorobenzene (1.0 mmol), $Pd(OAc)_2$ (2 mol%), **L** (8 mol%; for diphosphine, 4 mol%), K_2CO_3 (0.75 mmol), and dioxane (1 mL) were stirred at 100 °C for 16 h under N_2. GC yields were reported using dodecane as the internal standard. [b]The reaction was carried out at 105 °C).

To develop a general and effective catalyst system for direct C–H arylation in generating tetra-*ortho*-substituted biaryls, we started to investigate the capability of using triarylphosphine in this sterically congested reaction. Sterically hindered di-*ortho*-substituted 2-chloro-1,3-dimethylbenzene (**1a**) and pentafluorobenzene (**2a**) were chosen as the benchmark substrates for our initial screening (Scheme 2). Our previously reported indolylphosphine ligands, where the $-PPh_2$ group attaching to different positions of the indole ring (**L1**-**L6**) were examined.[19] Ligand **L5** showed excellent catalytic activity towards this coupling reaction and 98% product yield was obtained. Other commercially available and well-recognized phosphines, such as Ph_3P, dppm, dppe, dppp, dppf, BINAP, XantPhos, **L7**, **L8**, **L9** and **L10** were further evaluated. **L9** gave a comparable product yield to **L5**. When the catalyst loading was reduced to 0.25 mol% Pd and the reactions were conducted at 105 °C, **L9** afforded a better product yield (99% from **L9** *vs* 78% from **L5**).[20] It is interesting to show that the original Buchwald-type ligand scaffolds bearing $-PCy_2$ moiety, for examples, CyJohnPhos, DavePhos, SPhos, and XPhos gave only moderate product yields. Thus, it is believed that synthesis of tetra-*ortho*-substituted polyfluoroarenes from aryl chloride is highly sensitive to the bulkiness and electron-richness of the ligands.

Table 1. Optimization of Reaction Conditions for Pd-Catalyzed Direct Arylation of Pentafluorobenzene with Sterically Hindered Aryl Chloride[a]



entry	Pd source (mol% Pd)	base	solvent	% yield[b]
1	$Pd(OAc)_2$ (0.25)	K_2CO_3	dioxane	99
2	$Pd(TFA)_2$ (0.25)	K_2CO_3	dioxane	40
3	$PdCl_2(CH_3CN)_2$ (0.25)	K_2CO_3	dioxane	18

4	$Pd_2(dba)_3$ (0.25)	K_2CO_3	dioxane	21
5[c]	$Pd(OAc)_2$ (0.25)	K_2CO_3	dioxane	10
6[d]	$Pd(OAc)_2$ (0.25)	K_2CO_3	dioxane	25
7[e]	$Pd(OAc)_2$ (0.25)	K_2CO_3	dioxane	76
8	$Pd(OAc)_2$ (0.25)	Na_3PO_4	dioxane	trace
9	$Pd(OAc)_2$ (0.25)	K_3PO_4	dioxane	6
10	$Pd(OAc)_2$ (0.25)	Na_2CO_3	dioxane	trace
11	$Pd(OAc)_2$ (0.25)	KOAc	dioxane	trace
12	$Pd(OAc)_2$ (0.25)	K_2CO_3	toluene	10
13	$Pd(OAc)_2$ (0.25)	K_2CO_3	DMA	trace
14	$Pd(OAc)_2$ (0.25)	K_2CO_3	*i*-PrOAc	51
15[f]	$Pd(OAc)_2$ (0.25)	K_2CO_3	dioxane	64

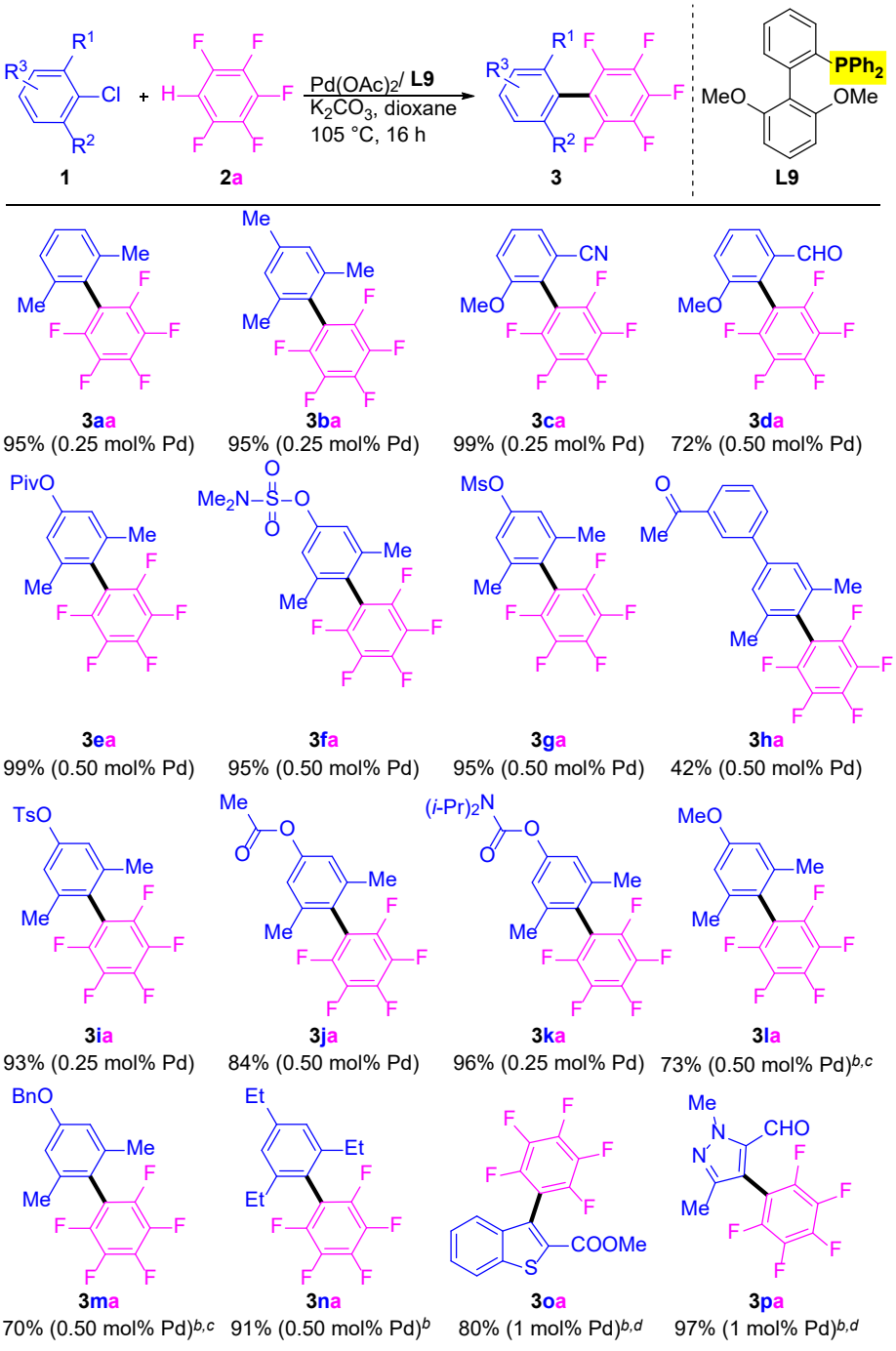
[a]Reaction conditions: 2-Chloro-1,3-dimethylbenzene (0.5 mmol), pentafluorobenzene (1.0 mmol), Pd source (0.25 mol%), **L9** (1 mol%), base (0.75 mmol), and solvent (1 mL) were stirred at 105 °C for 16 h under N_2. [b]GC yields were reported using dodecane as the internal standard. [c]$Pd(OAc)_2$: **L9** = 1:1. [d]$Pd(OAc)_2$: **L9** = 1:2. [e]$Pd(OAc)_2$: **L9** = 1:3. [f]Pivalic acid (10 mol%) was added.

Having identified the best ligand, we further optimized reaction conditions for this cross-coupling reaction (Table 1). Among the palladium sources surveyed, $Pd(OAc)_2$ was found to be the most suitable palladium precursor (Table 1, entries 1-4). Upon varying the Pd/ligand ratio from 1:1 to 1:4, the ratio of 1:4 provided the highest product yield (Table 1, entries 1 and 5-7). Commonly used inorganic bases were also screened (Table 1, entries 1 and 8-11). K_2CO_3 showed the superior result. Dioxane was found to be the best solvent of choice in this reaction (Table 1, entries 1 and 12-14). Addition of pivalic acid additive gave lower product yield (Table 1, entries 1 vs 15).

With the optimized reaction conditions in hand, we next evaluated the efficacy of this catalyst system in the direct arylation of pentafluorobenzene using sterically hindered aryl chlorides (Table 2). A wide range of activated and deactivated sterically hindered aryl chlorides were examined. An array of common functional groups such as nitrile, aldehyde, methyl ester, ketone, sulfonate, sulfonamide and

amide were compatible under these mild reaction conditions (Table 2, products **3ca**, **3da**, **3ea**, **3fa**, **3ga**, **3ha**, **3ia**, **3ja** and **3ka**). Even deactivated *para*-methoxy-substituted sterically hindered aryl chlorides were found to be feasible cross-coupling partners (Table 2, products **3la** and **3ma**). Extremely sterically congested 2,4,6-triethyl-substituted aryl chloride reacted smoothly and gave the corresponding product in excellent yield (Table 2, product **3na**). In addition to a variety of sterically hindered aryl chlorides, heteroaryl chlorides with di-*ortho*-substituents were investigated (Table 2, products **3oa** and **3pa**). Good-to-excellent product yields were afforded.

Table 2. Palladium-Catalyzed Direct Arylation of Pentafluorobenzene with Sterically Hindered Aryl Chlorides[a]

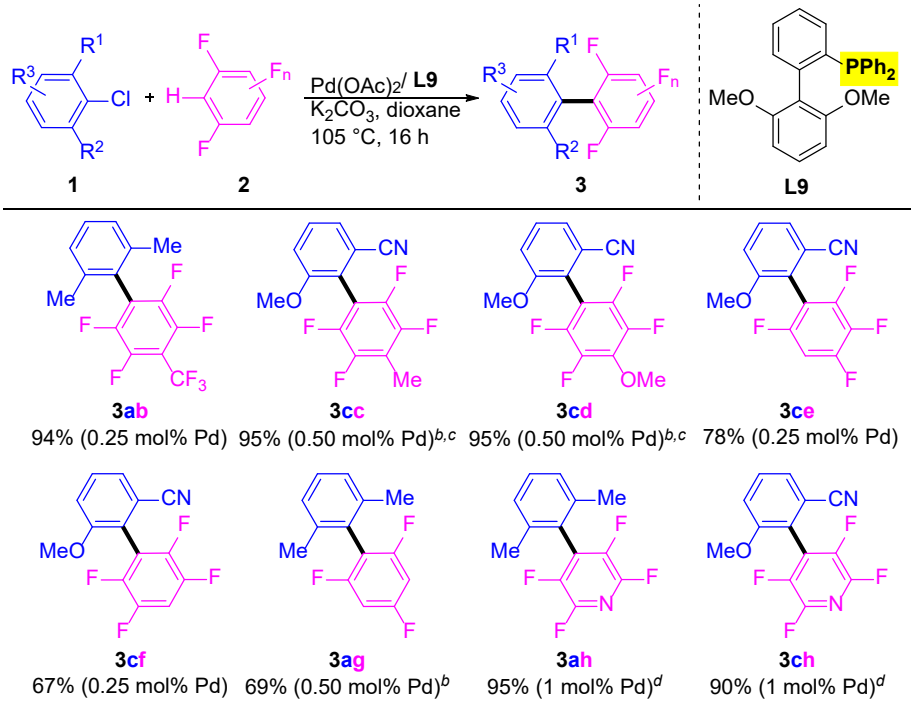


[a]Reaction conditions: sterically hindered aryl chlorides (0.5 mmol), pentafluorobenzene (1.0 mmol), $Pd(OAc)_2$:**L9** (1:4), K_2CO_3 (0.75 mmol), and dioxane (1 mL) were stirred at 105 °C for 16 h under N_2. Isolated yields were reported. Reaction times were not optimized for each substrate. [b]The reaction was

conducted at 110 °C. [c]The reaction was conducted for 24 h. [d]The reaction was conducted for 18 h.

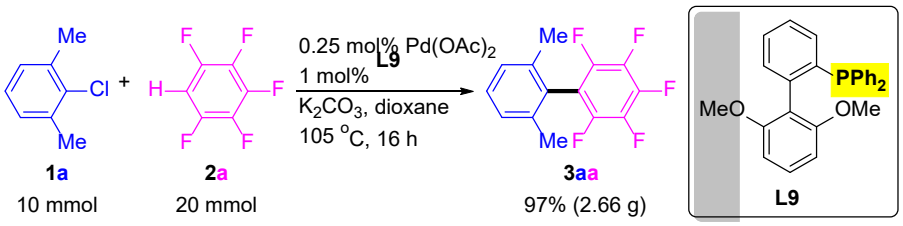
To further expand the substrate scope, we next investigated other polyfluorarenes as the cross-coupling partners (Table 3). *p*-Me, *p*-OMe, *p*-CF_3 substituted tetrafluoroarenes and trifluoroarene were found to be applicable substrates (**3ab**, **3cc**, **3cd**, **3ce**, **3cf** and **3ag**). Polyfluoropyridine was able to couple with sterically hindered aryl chlorides to afford the desired product in good-to-excellent yields (**3ah** and **3ch**).

Table 3. Palladium-Catalyzed Direct Arylation of Polyfluoroarenes with Sterically Hindered Aryl Chlorides[a]



[a]Reaction conditions: Sterically hindered aryl chlorides (0.5 mmol), polyfluoroarenes (1.0 mmol), $Pd(OAc)_2$:**L9** (1:4), K_2CO_3 (0.75 mmol), and dioxane (1 mL) were stirred at 105 °C for 16 h under N_2. Isolated yields were reported. Reaction times were not optimized for each substrate. [b]4 equiv. polyfluorobenzene was added. [c]The reaction was conducted for 24 h. [d]The reaction was conducted at 110 °C.

To test the feasibility of scaling up the current reaction conditions, a gram-scale direct C–H arylation of pentafluorobenzene with 2-chloro-1,3-dimethylbenzene was conducted (Scheme 3). It afforded the desired coupling product essentially without reducing the percentage yield.



Scheme 3. The Gram-Scale Cross-Coupling Reaction (Reaction conditions: 2-Chloro-1,3-dimethylbenzene (10 mmol), pentafluorobenzene (20 mmol), $Pd(OAc)_2$ (0.25 mol%), **L9** (1 mol%), K_2CO_3 (15 mmol), and dioxane (20 mL) were stirred at 105 °C for 16 h under N_2. Isolated yield was reported.)

Conclusion

In conclusion, we reported the first general palladium-catalyzed direct C-H arylation of polyfluoroarenes for difficult tetra-*ortho*-substituted biaryl synthesis. Good functional compatibility was observed under these reaction conditions, and the catalyst loading could be as low as 0.25 mol% of palladium catalyst. Key to success of this finding is the use of Buchwald-type biaryl ligand scaffold bearing only the $–PPh_2$ moiety, instead of $–PCy_2$ group, as the ligand. Particularly noteworthy is that this $–PPh_2$-containing ligand **L9** displays even higher performance than the original SPhos. We believe this research outcome will gain a new insight of employing $–PPh_2$-containing phosphine (triarylphosphine) in other sterically hindered aryl chloride cross-coupling reactions.

Experimental Section

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All arylation reactions were performed in resealable screw-capped Schlenk flask (approx. 20 mL volume) in the presence of Teflon-coated magnetic stirrer bar (4.5 mm × 12 mm). Dioxane, and toluene were freshly distilled from sodium and sodium benzophenone ketyl under nitrogen.[21] Anhydrous *N*,*N*-dimethylacetamide (DMA) in Sure/Seal bottles was purchased from Aldrich and used directly. Isopropyl acetate (*i*-PrOAc) was freshly distilled from anhydrous $CaCl_2$ under nitrogen. K_3PO_4, K_2CO_3, Na_3PO_4, KOAc and Na_2CO_3 were purchased from commercial suppliers and used as received. $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$ and $Pd_2(dba)_3$ were purchased from Strem and $Pd(TFA)_2$ was purchased from Aldrich. Indolyl phosphine ligands **L1**,[19a] **CM-Phos**,[22] **L2-L5**[19c] and **L6**[19d] were

prepared according to the reported literatures respectively. Ligands **PPh_3**, **dppm**, **dppe**, **dppp**, **dppf**, **BINAP**, **XantPhos**, **L7**, **L8**, **XPhos**, **SPhos**, **DavePhos** and **CyJohnPhos** were purchased from commercial suppliers. Ligands **L9** and **L10** were prepared according to the reported literature.[23] Thin layer chromatography was conducted on Merck pre-coated silica gel 60 F_{254} plates. Silica gel (Merck, 230-400 mesh) was used for column chromatography. Melting points were measured on an uncorrected Büchi Melting Point B-545 instrument. NMR spectra were obtained on a Brüker spectrometer (400 or 500MHz for ^1H, 100 or 125 MHz for ^{13}C and 376 MHz for ^{19}F). Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), or with tetramethylsilane (TMS, δ 0.00 ppm) acted as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak). ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as the external standard and low field is positive. Coupling constants (J) were reported in Hertz (Hz). Mass spectra (EI-MS and ESI-MS) were recorded on a HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Agilent 6540 ESI-QTof-MS and a Waters GCT Premier EI-ToF-MS. GC-MS analysis was performed on a HP 5977A GCD system using a HP5MS column (30 m × 0.25 mm). The products reported in GC yield were referred to the authentic samples/dodecane calibration standard from HP 7890B GC-FID system. All isolated yield of compounds were estimated to be greater than 95% purity according to capillary gas chromatography (GC) or ^1H NMR measurement. Compounds described in the literature were characterized by comparison of their ^1H, ^{13}C and ^{19}F NMR spectra to the previously reported data. The procedures in this section are representative, and thus the yields may differ from those reports in tables.

General procedure for initial ligand screenings (Pd catalysts loading equal to 2.0 mol%): $Pd(OAc)_2$ (2 mol%, 2.2 mg), ligand (Pd : L = 1 : 4) and K_2CO_3 (0.75 mmol, 0.104 g) were added into Schlenk tubes equipped with a Teflon-coated magnetic stir bar, and sealed with screw cap. The tubes were carefully evacuated and backfilled with nitrogen (3 cycles). Pentafluorobenzene (1.0 mmol, 111 μL), 2-chloro-1,3-dimethylbenzene (0.5 mmol, 67 μL) and freshly distilled 1 mL dioxane were added via syringe carefully under nitrogen. The reaction mixture was stirred for 1 min at room temperature. The tube was then placed into a preheated oil bath (100 °C) and stirred for 16 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (114 μ L, internal standard) and water (~3 mL) were added. The organic layer was subjected to GC. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

General procedure for initial ligand screenings (Pd catalysts loading equal to 0.25 mol%): A stock solution of $Pd(OAc)_2$ (2 mol%, 2.2 mg) with ligand (8 mol%) in freshly distilled 8 mL dioxane (0.25

mol% Pd per 1 mL stock solution) was initially prepared under N_2 with stirring up to dissolve all of the solids at room temperature. K_2CO_3 (0.75 mmol, 0.104 g) was charged to Schlenk tube with magnetic stirrer bar. Each tube was carefully evacuated and backfilled with nitrogen (3 cycles). Pentafluorobenzene (1.0 mmol, 111 μL), 2-chloro-1,3-dimethylbenzene (0.5 mmol, 67 μL) and the corresponding volume of stock solution of palladium complex were added by syringe carefully under nitrogen. The batch of Schlenk tubes was resealed and was stirred for 1 min at room temperature. The tube was then placed into a preheated oil bath (100-105 °C) and stirred for 16 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (114 μ L, internal standard) and water (~3 mL) were added. The organic layer was subjected to GC. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

General procedure for reaction condition screening (Pd catalysts loading equal to 0.25 mol%): A stock solution of $Pd(OAc)_2$ (2 mol%, 2.2 mg) with ligand **L9** (8 mol%, 15.9 mg) in freshly distilled 8 mL solvent (0.25 mol% Pd per 1 mL stock solution) was initially prepared under N_2 with stirring up to dissolve all of the solids at room temperature. Base (0.75 mmol) was charged to Schlenk tube with magnetic stirrer bar. Each tube was carefully evacuated and backfilled with nitrogen (3 cycles). Pentafluorobenzene (1.0 mmol, 111 μL), 2-chloro-1,3-dimethylbenzene (0.5 mmol, 67 μL) and the corresponding volume of stock solution of palladium complex were added by syringe carefully under nitrogen. The batch of Schlenk tubes was resealed and was stirred for 1 min at room temperature. The tube was then placed into a preheated oil bath (105 °C) and stirred for 16 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (114 μ L, internal standard) and water (~3 mL) were added. The organic layer was subjected to GC. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

General procedure for direct arylation of polyfluoroarenes with sterically hindered aryl chlorides (Pd catalysts loading ranged from 0.25 to 1.0 mol%): A stock solution of $Pd(OAc)_2$ (2 mol%, 2.2 mg) with ligand **L9** (8 mol%, 15.9 mg) in freshly distilled 8 mL dioxane (0.25 mol% Pd per 1.00 mL stock solution) was initially prepared under N_2 with stirring up to dissolve all of the solids at room temperature. Sterically hindered aryl chlorides (if solid, 0.5 mmol), K_2CO_3 (0.75 mmol, 0.104 g) were charged to Schlenk tube equipped with magnetic stirrer bar. Each tube was carefully evacuated and backfilled with nitrogen (3 cycles). Polyfluoroarenes (1.0-2.0 mmol), sterically hindered aryl chlorides (if liquid, 0.5 mmol) and the corresponding volume of stock solution of palladium complex were added by syringe carefully under nitrogen. Further solvent (if needed) was added up to the final volume 1.0 mL. The tube was resealed and was stirred for 1 min at room temperature. The tube was then placed into a preheated oil bath (105-110 °C) and stirred for 16-24 h. After the completion of the reaction, the

reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

General procedure for gram-scale cross-coupling reaction: $Pd(OAc)_2$ (0.25 mol%, 5.6 mg), ligand **L9** (1 mol%, 39.8 mg) and K_2CO_3 (15 mmol, 2.07 g) were added into 80 mL Schlenk tube equipped with a Teflon-coated magnetic stir bar, and sealed with screw cap. The tube was carefully evacuated and backfilled with nitrogen (3 cycles). Pentafluorobenzene (20 mmol, 2.23 mL), 2-chloro-1,3-dimethylbenzene (10 mmol, 1.33 mL) and freshly distilled 20 mL dioxane were added via syringe carefully under nitrogen. The reaction mixture was stirred for 1 min at room temperature. The tube was then placed into a preheated oil bath (100 °C) and stirred for 16 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~100 mL) and water (~30 mL) were added. The organic layer was subjected to GC. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

4-Chloro-3,5-dimethylphenyl pivalate

4-Chloro-3,5-dimethylphenyl pivalate was prepared according to the reported procedure.[24] 4-Chloro-3,5-dimethylphenol (20 mmol), triethylamine (100 mmol) and PivCl (30 mmol) in anhydrous DCM (80 mL) were given white solid product (3.77 g, 78%). Eluents (Ethyl acetate: Hexane = 1: 4, R_f= 0.80) was used for flash column chromatography. m.p. 43.2-44.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.37 (s, 6H), 6.81 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 27.1, 39.0, 121.2, 131.4, 137.3, 148.6, 177.1; MS (EI): m/z (relative intensity) 240.2 (M^+, 23), 156.1 (100), 121.1 (26), 91.1 (14), 57.1 (51); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}ClO_2$ 241.0990; Found 241.0994.

4-Chloro-3,5-dimethylphenyl dimethylsulfamate

4-Chloro-3,5-dimethylphenyl dimethylsulfamate was prepared according to the reported procedure with a modification. [25] 4-Chloro-3,5-dimethylphenol (20 mmol), KOH (50 mmol) and *N*,*N*-dimethylsulfamoyl chloride (25 mmol) in anhydrous THF (80 mL) were given white solid product (3.99 g, 76%). Eluents (Ethyl acetate: Hexane = 1: 4, R_f= 0.50) was used for flash column chromatography. m.p. 64.8-66.2°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 6H), 2.98 (s, 6H), 7.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 38.7, 121.3, 132.6, 137.8, 147.7; MS (EI): m/z (relative intensity) 263.1 (M^+, 100), 183.1 (18), 155.0 (68), 127.0 (40), 108.0 (62), 91.1 (26); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}ClNO_3S$ 264.0456; Found 264.0461.

4-Chloro-3,5-dimethylphenyl methanesulfonate

4-Chloro-3,5-dimethylphenyl methanesulfonate was prepared according to the reported procedure.[26] 4-Chloro-3,5-dimethylphenol (20 mmol), triethylamine (200 mmol) and MsCl (40 mmol) in anhydrous DCM (40 mL) were given white solid product (3.51 g, 75%). Eluents (Ethyl acetate: Hexane = 1: 4, R_f= 0.50) was used for flash column chromatography. m.p. 77.2-79.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 6H), 3.16 (s, 3H), 7.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 37.4, 121.6, 133.4, 138.3, 146.6; MS (EI): m/z (relative intensity) 234 (M^+, 65), 155 (100), 127 (80), 91 (70); HRMS (EI-TOF) m/z: M^+ Calcd for $C_9H_{11}O_3SCl$ 234.0125; Found 234.0117.

4-Chloro-3,5-dimethylphenyl diisopropylcarbamate

4-Chloro-3,5-dimethylphenyl diisopropylcarbamate was prepared according to the reported procedure.[27] 4-Chloro-3,5-dimethylphenol (20 mmol), K_2CO_3 (30 mmol) and *N*,*N*-diisopropylcarbamoyl chloride (30 mmol) in anhydrous ACN (100 mL) were given white solid product (5.1 g, 90%). Eluents (Ethyl acetate: Hexane = 1: 4, R_f= 0.70) was used for flash column chromatography. m.p. 77.5-78.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (bs, 12H), 2.36 (s, 6H), 3.92-4.09 (m, 2H), 6.86 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.7, 21.5, 45.9, 46.9, 121.7, 130.8, 137.1, 148.9, 153.8; MS (EI): m/z (relative intensity) 283.1 (M^+, 6), 156.0 (63), 128.1 (89), 86.1 (100); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{23}ClNO_2$ 284.1412; Found 284.1421.

2,3,4,5,6-Pentafluoro-2',6'-dimethyl-1,1'-biphenyl (Table 2, compound 3aa)[28]

Yield: 95% (129 mg). Eluents (Hexane, R_f= 0.70) was used for flash column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 6H), 7.20 (d, *J*= 7.6 Hz, 2H) and 7.32 (t, *J*= 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 113.8-114.5 (m), 125.6, 127.7, 129.4, 136.3-136.7(m), 137.4, 138.7-139.1 (m), 139.2-139.4 (m), 141.7-142.0 (m), 142.3-142.6 (m), 144.8-145.0 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.0- -161.9 (m, 2F), -155.2 (t, *J*= 22.0 Hz, 1F), -140.2 (dd, *J*= 24.4 Hz, 9.4 Hz, 2F); MS (EI): m/z (relative intensity) 272.1 (M^+, 100), 257.1 (65), 237.1 (53), 219.1 (7), 201.1 (9), 188.1(8).

2,3,4,5,6-Pentafluoro-2',4',6'-trimethyl-1,1'-biphenyl (Table 2, compound 3ba)[13a]

Yield: 95% (136 mg). Eluents (Hexane, R_f= 0.70) was used for flash column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 6H), 2.40 (s, 3H), 7.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.1, 114.2-114.6 (m), 122.6, 128.6, 136.3-136.7 (m), 137.2, 138.8-139.0 (m), 139.1-139.2 (m), 139.3, 141.7-142.1 (m), 142.4-142.7 (m), 144.9-145.2 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.2- -162.1 (m, 2F), -155.5 (t, *J*= 20.7, 1F), -140.2 (dd, *J*= 22.7 Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 286.1 (M^+, 100), 271.1 (76), 251.1 (28)), 237.1 (10), 219.1 (5), 201.1 (10).

2',3',4',5',6'-Pentafluoro-6-methoxy-[1,1'-biphenyl]-2-carbonitrile (Table 2, compound 3ca)

Yield: 99% (148 mg). Eluents (Ethyl acetate: Hexane = 1: 5, R_f= 0.70) was used for flash column chromatography. Pale yellow solid; m.p. 70.6 – 71.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.29 (d, *J*= 8.6 Hz, 1H), 7.42 (d, *J*= 7.6 Hz, 1H), 7.60 (t, *J*=8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 108.7-109.1 (m), 115.2, 115.7, 116.7, 118.8, 124.7, 131.8, 136.3-136.6 (m), 138.7-139.2 (m), 140.2-140.5 (m), 142.7-143.0 (m), 143.1-143.3 (m), 145.5-145.8 (m), 157.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.9- -161.7 (m, 2F), -152.9 (t, *J*= 20.7 Hz, 1F), -138.6 (dd, *J*= 22.3 Hz, 8.5 Hz, 2F); MS (EI): m/z (relative intensity) 299.1 (M^+, 100), 284.1 (10), 256.1 (32), 236.1 (10), 218.1 (6), 205.0 (9), 143.0 (10); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{14}H_6F_5NO$ 299.0364; Found 299.0374.

2',3',4',5',6'-Pentafluoro-6-methoxy-[1,1'-biphenyl]-2-carbaldehyde (Table 2, compound 3da)

Yield: 72% (109 mg). Eluents (Ethyl acetate: Hexane = 1: 20, R_f= 0.40) was used for flash column chromatography. White solid; m.p. 63.8 – 67.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 7.29 (d, *J*= 7.9 Hz, 1H), 7.60-7.67 (m, 2H) 9.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 108.7-109.1 (m), 115.9, 116.6, 132.2, 131.4, 135.4, 136.1-136.4 (m), 138.6-138.9 (m), 139.6-140.0 (m), 142.2-142.5 (m), 143.0-143.3 (m), 145.6-145.7 (m), 157.6, 190.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.9- -162.7 (m, 2F), -154.5 (t, *J*= 20.7 Hz, 1F), -139.4 (dd, *J*= 22.9 Hz, 7.7 Hz, 2F); MS (EI): m/z (relative intensity) 302.1 (M^+, 100), 281.1 (23), 258.0 (22), 231.0 (22), 211.0 (26); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{14}H_7F_5O_2$ 302.0361; Found 302.0367..

2',3',4',5',6'-Pentafluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl pivalate (Table 2, compound 3ea)

Yield: 99% (184 mg). Eluents (Ethyl acetate: Hexane = 1: 30, R_f= 0.30) was used for flash column chromatography. White solid; m.p. 105.2 – 107.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.08 (s, 6H), 6.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 27.1, 39.1, 113.4-113.9 (m), 120.7, 122.9, 136.4-136.7 (m), 139.0, 139.3-139.7 (m), 142.5-142.7 (m), 144.9-145.2 (m), 151.7, 176.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.8- -161.7 (m, 2F), -154.8 (t, *J*= 20.7 Hz, 1F), -139.8 (dd, *J*= 24.4 Hz, 9.4 Hz, 2F); MS (EI): m/z (relative intensity) 372.2 (M^+, 18), 288.1 (100), 271.1 (11), 253.1 (6), 85.1 (10), 57.1 (26); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{19}H_{17}F_5O_2$ 372.1143; Found 372.1159.

2',3',4',5',6'-Pentafluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl dimethylsulfamate (Table 2, compound 3fa)

Yield: 95% (188 mg). Eluents (Ethyl acetate: Hexane = 1: 10, R_f= 0.23) was used for flash column chromatography. White solid; m.p. 100.0 – 103.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 6H), 3.01 (s, 6H), 7.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 38.8, 113.1-113.5 (m), 120.6, 124.0, 136.4-136.7 (m), 138.9-139.2 (m), 139.4-139.5 (m), 139.7, 142.0-142.3 (m), 142.5-142.6 (m), 144.9-145.1 (m),

150.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.6- -161.4 (m, 2F), -154.3 (t, *J*= 20.7 Hz, 1F), -139.9 (dd, *J*= 22.6 Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 395.1 (M^+, 100), 315.1 (30), 287.1 (29), 259.1 (12), 219.1 (14), 181.0 911), 108.0 (76); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}F_5NO_3S$ 396.0687; Found 396.0705.

2',3',4',5',6'-Pentafluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl methanesulfonate (Table 2, compound 3ga)

Yield: 95% (174 mg). Eluents (Ethyl acetate: Hexane = 1: 5, R_f= 0.29) was used for flash column chromatography. White solid; m.p. 146.5 – 147.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H), 3.18 (s, 3H), 7.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 37.6, 112.8-113.2 (m), 120.9, 124.9, 136.3-136.7 (m), 138.9-139.3 (m), 139.6-139.8 (m), 140.0, 142.2-142.5 (m), 144/7-145.1 (m), 149.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.4- -161.2 (m, 2F), -154.0 (t, *J*= 20.7 Hz, 1F), -139.8 (dd, *J*= 24.4 Hz, 9.4 Hz, 2F); MS (EI): m/z (relative intensity) 366.1 (M^+, 63), 288.1 (100), 259.1(18), 219.0 (12), 181.0 (12), 91.1 (10); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{15}H_{11}F_5O_3S$ 366.0344; Found 366.0339.

1-(2'',3'',4'',5'',6''-Pentafluoro-3',5'-dimethyl-[1,1':4',1''-terphenyl]-3-yl)ethanone (Table 2, compound 3ha)

Yield: 42% (82.0 mg). Eluents (Ethyl acetate: Hexane = 1: 9, R_f= 0.22) was used for flash column chromatography. White solid; m.p. 145.1 – 145.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 6H), 2.67 (s, 3H), 7.42 (s, 2H), 7.55 (t, *J*= 7.7 Hz, 2H), 7.81-7.83 (m, 1H), 7.94-7.97 (m, 1H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 26.6, 113.7-114.1 (m), 125.1, 126.5, 126.9, 127.5, 129.0, 131.7, 136.3-136.6 (m), 137.6, 138.1, 138.7-139.1 (m), 140.9, 141.2, 141.8-142.2 (m), 142.5-142.6 (m), 144.8-145.1 (m), 197.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.7- -161.5 (m, 2F), -154.7 (t, *J*= 20.7 Hz, 1F), -139.9 (dd, *J*= 24.4 Hz, 9.4 Hz, 2F); MS (EI): m/z (relative intensity) 390.3 (M^+, 66), 375.1 (100), 332.1 (27), 311.1 (7), 187.6 (7); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{22}H_{15}F_5O$ 390.1038; Found 390.1024.

2',3',4',5',6'-Pentafluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl 4-methylbenzenesulfonate (Table 2, compound 3ia)

Yield: 93% (206 mg). Eluents (Ethyl acetate: Hexane = 1: 20, R_f= 0.50) was used for flash column chromatography. White solid; m.p. 142.7 – 144.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 6H), 2.45 (s, 3H), 6.83 (s, 2H), 7.34 (d, *J*= 8.08 Hz, 2H), 7.76 (d, *J*= 8.32 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.6, 112.9-113.3 (m), 121.2, 124.4, 128.4, 129.7, 132.5, 136.3-136.6 (m), 138.9-139.1 (m), 139.5, 142.2-142.5 (m), 144.8-145.0 (m), 145.5, 150.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.6- -161.4 (m, 2F), -154.3 (t, *J*= 20.7 Hz, 1F), -139.9 (dd, *J*= 23.3 Hz, 16.9 Hz, 2F); MS (EI): m/z (relative intensity) 442.1 (M^+, 44), 350.1 (12), 287.1 (6), 219.1 (7), 181.0 (7), 155.0 (100), 91.1 (98); HRMS (ESI-TOF) m/z: [M

+ Na]$^+$ Calcd for $C_{21}H_{15}F_5O_3SNa$ 465.0554; Found 465.0563.

2',3',4',5',6'-Pentafluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl acetate (Table 2, compound 3ja)

Yield: 84% (139 mg). Eluents (Ethyl acetate: Hexane = 1: 9, R_f= 0.65) was used for flash column chromatography. White solid; m.p. 130.8 – 131.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 2.30 (s, 3H), 6.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.0, 113.4-113.8 (m), 120.7, 123.1, 136.3-136.7 (m), 139.1, 139.2-139.5 (m), 141.9-142.2 (m), 142.5-142.7 (m), 144.9-145.1 (m), 151.2, 169.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.9- -161.7 (m, 2F), -154.8 (t, *J*= 20.1 Hz), -139.7 (dd, *J*= 24.4 Hz, 9.4 Hz); MS (EI): m/z (relative intensity) 330.1 (M^+, 6), 288.1 (100), 271.1 (13), 253.1 (7); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{16}H_{11}F_5O_2$ 330.0674; Found 330.0668.

2',3',4',5',6'-Pentafluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl diisopropylcarbamate (Table 2, compound 3ka)

Yield: 96% (199 mg). Eluents (Ethyl acetate: Hexane = 1: 9, R_f= 0.25) was used for flash column chromatography. White solid; m.p. 78.2 – 81.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27-1.39 (m (broad), 12H), 2.08 (s, 6H), 3.98-4.10 (m (broad), 2H), 6.97 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.3, 21.4, 46.1, 46.9, 113.6-114.0 (m), 121.0, 122.2, 136.3-136.5 (m), 138.7, 138.8-139.3 (m), 141.7-142.0 (m), 142.4-142.5 (m), 145.0-145.1 (m), 151.9, 153.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.1- -161.9 (m, 2F), -155.1 (t, *J*= 20.7 Hz, 1F), -139.7 (dd, *J*= 22.6 Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 415.2 (M^+, 1), 288.1 (65), 271.1 (11), 253.1 (9), 128.1 (100), 86.1 (91); HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{22}F_5NO_2Na$ 438.1463; Found 438.1473.

2,3,4,5,6-Pentafluoro-4'-methoxy-2',6'-dimethyl-1,1'-biphenyl (Table 2, compound 3la)[29]

Yield: 73% (110 mg). Eluents (DCM: Hexane = 1: 30, R_f= 0.5) was used for flash column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 3.84 (s, 3H), 6.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 55.1, 113.2, 114.1-114.5 (m), 117.7, 136.3-136.7 (m), 138.9, 139.0-139.3 (m), 141.6-142.0 (m), 142.7-142.9 (m), 145.2-145.4 (m), 160.2, ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.3- -162.2 (m, 2F), -155.5 (t, *J*= 20.7 Hz, 1F), -140.0 (dd, *J*= 22.6 Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 302.1 (M^+, 100), 283.1 (15), 257.1 (10), 237.1 (11), 181.0 (6).

4'-(Benzyloxy)-2,3,4,5,6-pentafluoro-2',6'-dimethyl-1,1'-biphenyl (Table 2, compound 3ma)

Yield: 70% (132 mg). Eluents (Ethyl acetate: Hexane = 1: 20, R_f= 0.50) was used for flash column chromatography. White solid; m.p. 99.8 – 101.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H), 5.11 (s, 2H), 6.85 (s, 2H), 7.38-7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 69.9, 114.0, 114.2-114.4 (m), 117.9, 127.5, 128.0, 128.6, 136.4-136.6 (m), 136.8, 138.9, 141.6-142.0 (m), 142.7-142.9 (m), 145.1-

145.4 (m), 159.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.2- -162.0 (m, 2F), -155.3 (t, *J*= 20.7 Hz, 1F), -139.9 (dd, *J*= 22.6 Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 378.2 (M^+, 32), 287.1 (2), 219.1 (2), 181.0 (2), 91.1 (100), 65.1 (7); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{21}H_{15}F_5O$ 378.1043; Found 378.1037.

2',4',6'-Triethyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl (Table 2, compound 3na)

Yield: 91% (149 mg). Eluents (Hexane, R_f= 0.61) was used for flash column chromatography. Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09-1.14 (m, 6H), 1.32-1.37 (m, 3H), 2.34-2.41 (m, 4H), 2.72-2.77 (m, 2H), 7.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 15.1, 26.9, 28.7, 114.1-114.5 (m), 121.3, 125.8, 136.3-136.5 (m), 138.8-139.1 (m), 139.2-139.5 (m), 141.7-142.0 (m), 142.8-143.1 (m), 143.2, 145.1-145.5 (m), 145.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.3- -162.1 (m, 2F), -155.5- -155.4 (m, 1F), -139.1 (dd, *J*= 24.4 Hz, 9.4 Hz, 2F); MS (EI): m/z (relative intensity) 328.2 (M^+, 91), 313.1 (70), 299.1 (100), 271.1 (11), 251.1 (13), 237.1 (14); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{18}H_{17}F_5$ 328.1245; Found 328.1252.

Methyl 3-(perfluorophenyl)benzo[*b*]thiophene-2-carboxylate (Table 2, compound 3oa)

Yield: 80% (143 mg). Eluents (DCM: Hexane = 1: 9, R_f= 0.50) was used for flash column chromatography. White solid; m.p. 110.0 – 112.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.42-7.56 (m, 3H), 7.92 (d, *J*= 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 109.0-109.4 (m), 122.8, 123.8, 125.5, 126.7, 127.7, 131.9, 136.2-136.6 (m), 138.0, 138.7-139.1 (m), 139.9-140.2 (m), 140.4, 142.5-142.9 (m), 143.1-143.3 (m), 145.5-145.8 (m), 161.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.2- -162.1 (m, 2F), -153.5 (t, *J*= 20.8 Hz, 1F), -138.4 (dd, *J*= 21.8 Hz, 8.3 Hz, 2F); MS (EI): m/z (relative intensity) 358.1 (M^+, 94), 327.1 (100), 299.1 (32), 280.1 (23), 255.1 (45); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{16}H_7F_5O_2S$ 358.0087; Found 358.0090.

1,3-Dimethyl-4-(perfluorophenyl)-1*H*-pyrazole-5-carbaldehyde (Table 2, compound 3pa)

Yield: 97% (141 mg). Eluents (Ethyl acetate: Hexane = 1: 4, R_f= 0.40) was used for flash column chromatography. Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.70 (s, 3H), 9.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 36.8, 103.2-103.6 (m), 120.1, 131.1, 136.4-136.7 (m), 138.9-139.3 (m), 141.3-141.5 (m), 143.1-143.3 (m), 143.8-144.1 (m), 145.6-145.8 (m), 151.6, 183.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -160.2- -160.0 (m, 2F), -149.3 (t, *J*= 21.4 Hz, 1F) , -137.3- -137.2 (m, 2F); MS (EI): m/z (relative intensity) 289.1 (M^+, 100), 271.1 (40), 243.1 (6), 218.1 (8), 192.1 (32); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_8F_5N_2O$ 291.0551; Found 291.0556.

2,3,5,6-Tetrafluoro-2',6'-dimethyl-4-(trifluoromethyl)-1,1'-biphenyl (Table 3, compound 3ab)

Yield: 94% (151 mg). Eluents (Hexane, R_f= 0.65) was used for flash column chromatography. White solid; m.p. 81.4 – 82.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 6H), 7.24 (d, *J*= 7.6 Hz, 2H), 7.36 (t, *J*= 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 123.9-124.3 (m), 125.4, 127.8, 129.8, 136.8, 142.6-142.7 (m), 142.9-143.1 (m), 145.0-145.2 (m), 145.5-145.7 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.7- -140.4 (m, 2F), -138.3- -138.2 (m, 2F), -56.3 (t, *J*= 21.6 Hz, 3F); MS (EI): m/z (relative intensity) 322.1 (M^+, 100), 303.1 (51), 287.1 (35), 237.1 (13), 219.1 (7); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{15}H_9F_7$ 322.0587; Found 322.0571.

2',3',5',6'-Tetrafluoro-6-methoxy-4'-methyl-[1,1'-biphenyl]-2-carbonitrile (Table 3, compound 3cc)

Yield: 95% (140 mg). Eluents (Ethyl acetate: Hexane = 1: 5, R_f= 0.24) was used for flash column chromatography. White solid; m.p. 141.6 – 142.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.83 (s, 3H), 7.26 (d, *J*= 8.6 Hz, 1H), 7.38 (d, *J*= 7.7 Hz, 1H), 7.53 (t, *J*= 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.61, 56.1, 110.7-111.1 (m), 115.1, 115.6, 116.8, 116.9-117.3, 120.2, 124.6, 131.3, 142.3-142.6 (m), 143.7-143.9 (m), 144.8-145.0 (m), 146.1-146.3 (m), 157.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.6 (dd, *J*= 22.1 Hz, 11.3 Hz, 2F), -141.2 (dd, *J*= 22.1 Hz, 12.4 Hz, 2F); MS (EI): m/z (relative intensity) 295.1 (M^+, 100), 278.1 (9), 260.1 (20), 231.1 (7), 143.0 (10); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{15}H_9F_4NO$ 295.0615; Found 295.0617.

2,3,5,6-Tetrafluoro-2',6'-dimethyl-4-(trifluoromethyl)-1,1'-biphenyl (Table 3, compound 3cd)

Yield: 95% (148 mg). Eluents (Ethyl acetate: Hexane = 1: 5, R_f= 0.17) was used for flash column chromatography. White solid; m.p. 89.5 – 90.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.16 (s, 3H), 7.27 (d, *J*= 8.6 Hz, 1H), 7.39 (d, *J*= 7.8 Hz, 1H), 7.55 (t, *J*= 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 61.9-62.0 (m), 106.6-107.0 (m), 115.2, 115.6, 116.9, 119.7, 124.6, 131.3, 138.8-138.9 (m), 139.5-139.7 (m), 141.9-142.2 (m), 143.1-143.4 (m), 145.6-145.8 (m), 157.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -158.1- -158.0 (m, 2F), -140.7- -140.6 (m, 2F); MS (EI): m/z (relative intensity) 311.1 (M^+, 100), 276.1 (4), 253.0 (7), 218.1 (7), 200.0 (4); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{15}H_9F_4NO_2$ 311.0564; Found 311.0555.

2',3',4',6'-Tetrafluoro-6-methoxy-[1,1'-biphenyl]-2-carbonitrile (Table 3, compound 3ce)

Yield: 78% (110 mg). Eluents (Ethyl acetate: Hexane = 1: 9, R_f= 0.20) was used for flash column chromatography. White solid; m.p. 106.2 – 107.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.87-6.94 (m, 1H), 7.25 (d, *J*= 8.4 Hz, 1H), 7.38 (d, *J*= 7.8 Hz, 1H), 7.53 (t, *J*= 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 100.7-101.3 (m), 108.7-109.2 (m), 115.2, 115.6, 116.9, 120.1, 124.6, 131.3, 135.9-136.3 (m), 138.4-138.8 (m), 147.8-148.1 (m), 149.7-150.1 (m), 150.3-150.5 (m), 152.3-152.6 (m), 153.2-153.4 (m), 155.6-155.9 (m), 157.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -164.7- -164.6 (m, 1F), -131.1

(dd, *J*= 21.5 Hz, Hz, 6.8 Hz, 1F), -130.8- -130.7 (m, 1F), -114.4 (d, *J*= 10.9 Hz, 1F); MS (EI): m/z (relative intensity) 281.1 (M^+, 100), 260.1 (11), 238.1 (26), 218.1 (9), 187.0 (5); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{14}H_7F_4NO$ 281.0458; Found 281.0448.

2',3',5',6'-Tetrafluoro-6-methoxy-[1,1'-biphenyl]-2-carbonitrile (Table 3, compound 3cf)

Yield: 67% (94.2 mg). Eluents (Ethyl acetate: Hexane = 1: 9, R_f= 0.25) was used for flash column chromatography. White solid; m.p. 97.6 – 98.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.15-7.23 (m, 1H), 7.29 (d, *J*= 8.4 Hz, 1H), 7.42 (d, *J*= 7.7 Hz, 1H), 7.58 (t, *J*= 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 106.4-106.9 (m), 114.4-114.7 (m), 115.0, 115.7, 116.7, 119.8, 124.7, 131.6, 142.6-142.8 (m), 144.5-144.7 (m), 144.8-145.3 (m), 147.0-147.3 (m), 157.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -139.4 (dd, *J*= 21.5 Hz, 12.9 Hz, 2F), -138.8 (dd, *J*= 22.8 Hz, 12.2 Hz, 2F); MS (EI): m/z (relative intensity) 281.1 (M^+, 100), 260.1 (11), 238.1 (26), 218.1 (15), 187.0 (8), 143.0 (11); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{14}H_7F_4NO$ 281.0458; Found 281.0442.

2,4,6-Trifluoro-2',6'-dimethyl-1,1'-biphenyl (Table 3, compound 3ag)

Yield: 69% (81.5 mg). Eluents (Hexane, R_f= 0.56) was used for flash column chromatography. White solid; m.p. 50.0 – 51.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 6H), 6.76-6.84 (m, 2H), 7.17 (d, *J*= 7.5 Hz, 2H), 7.25-7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 100.0-100.6 (m), 113.0-113.5 (m), 127.4, 127.8, 128.7, 137.5, 158.7-159.0 (m), 160.8-161.1 (m), 161.2-161.4 (m), 163.3-163.6 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.2 (t, *J*= 5.64 Hz, 1F), -109.0 (d, *J*= 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 236.1 (M^+, 100), 221.1 (68), 201.1 (36), 169.1 (45), 145.0 (2); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{14}H_{11}F_3$ 236.0807; Found 236.0806.

4-(2,6-Dimethylphenyl)-2,3,5,6-tetrafluoropyridine (Table 3, compound 3ah)

Yield: 95% (121 mg). Eluents (Hexane, R_f= 0.50) was used for flash column chromatography. White solid; m.p. 63.5 – 65.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 6H), 7.21 (d, *J*= 7.6 Hz, 2H), 7.34 (t, *J*= 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 125.2, 127.9, 130.0, 133.2-133.6 (m), 136.3, 137.7-138.1 (m), 140.3-140.6 (m), 142.4-142.7 (m), 144.8-145.1 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -141.6- -141.4 (m, 2F), -90.6- -90.4 (m, 2F); MS (EI): m/z (relative intensity) 255.2 (M^+, 100), 240.1 (55), 220.1 (49); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{13}H_9F_4N$ 255.0671; Found 255.0672.

3-Methoxy-2-(perfluoropyridin-4-yl)benzonitrile (Table 3, compound 3ch)

Yield: 90% (127 mg). Eluents (Ethyl acetate: Hexane = 2: 8, R_f= 0.27) was used for flash column chromatography. White solid; m.p. 98.0 – 99.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.34 (d, *J*= 8.6 Hz, 1H), 7.44 (d, *J*= 7.6 Hz, 1H), 7.64 (t, *J*= 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.3,

114.1, 116.0, 116.2, 117.8, 124.9, 127.0-127.4 (m), 132.6, 138.2-138.5 (m), 140.8-141.1 (m), 142.0-142.3 (m), 144.5-144.8 (m), 157.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -139.9- -139.7 (m, 2F), -90.4- -90.2 (m, 2F); MS (EI): m/z (relative intensity) 282.1 (M^+, 100), 261.1 (134), 239.1 (14), 219.1 (10), 204.1 (14); HRMS (EI-TOF) m/z: M^+ Calcd for $C_{13}H_6F_4N_2O$ 282.0416; Found 282.0406.

2,3,4,5,6-Pentafluoro-2',6'-dimethyl-1,1'-biphenyl (Scheme 3, compound 3aa)[28]

Yield: 97% (2.66 g). Eluents (Hexane, R_f= 0.70) was used for flash column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 6H), 7.18 (d, *J*= 7.6 Hz, 2H) and 7.29 (t, *J*= 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 114.1-114.5 (m), 125.6, 127.7, 129.4, 136.6-136.9(m), 137.4, 138.6-138.9 (m), 139.5-139.7 (m), 141.5-141.8 (m), 142.6-142.8 (m), 144.6-144.8 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.0- -161.8 (m, 2F), -155.1 (t, *J*= 20.7 Hz, 1F), -140.2 (dd, *J*= 22.6 Hz, 8.3 Hz, 2F); MS (EI): m/z (relative intensity) 272.1 (M^+, 100), 257.1 (65), 237.1 (53), 219.1 (7), 201.1 (9), 188.1(8).

Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS spectra of synthesized compounds (PDF) and X-ray crystallographic data for **L9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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