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Pd/PR_3-Catalyzed Cross-Coupling of Aromatic Carboxylic Acids with Electron-Deficient Polyfluoroarenes via Combination of Decarboxylation with sp^2 C−H Cleavage

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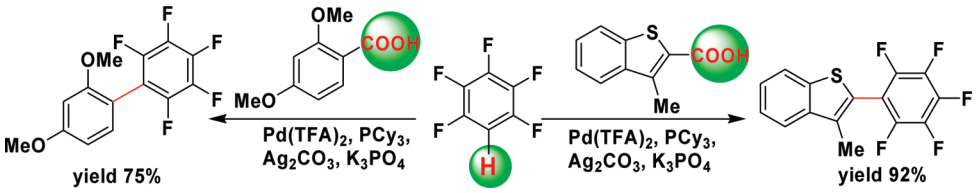

By using $Pd(TFA)_2/PCy_3$ as a catalyst, a broad range of aromatic carboxylic acids, including heteroaromatic carboxylic acids, efficiently underwent decarboxylative coupling with an array of polyfluoroarenes in the presence of stoichiometric amount of silver salts to generate biaryls. Silver salts were adjusted to the reactivity of aromatic carboxylic acids to efficiently suppress the protodecarboxylation and therefore improve decarboxylative cross-couplings. It was established that the palladium complex containing the PCy_3 ligand was capable of catalyzing the decarboxylation of electron-rich aromatic carboxylic acids, and silver salts promoted the decarboxylation of both electron-rich and -deficient ones. To explain the two different decarboxylation processes, two possible reaction pathways are proposed, which were further supported by the facts that the stoichiometric arylpalladium complex can directly arylate pentafluorobenzene in the presence of PCy_3 and the arylpalladium complex can catalyze the decarboxylative coupling of 2,4-dimethoxybenzoic acid with pentafluorobenzene. The kinetic isotope effect of 4.0 clearly showed that the C−H bond cleavage of polyfluoroarenes is involved in the rate-determining step.

Introduction

The biaryl motif is a key structural component in a number of natural products, medicinal compounds, and functional materials.[1] Consequently, the past decade has witnessed tremendous efforts in both academic and industrial laboratories devoted toward achieving efficient, high-yielding, and highly selective methods for construction of biaryl scaffolds. Thus far, transition-metal-catalyzed cross-coupling reactions (Suzuki, Stille, Kumada-Corriu, Negishi, and Hiyama) have evolved into the most commonly used tools for syntheses of biaryl compounds.[2] However, these traditional cross-coupling reactions inherently suffer from their lack of atom and step economy due to the requirement for use of two preactivated (synthesized) coupling partners, that is, aryl halides or triflates and expensive organometallic reagents. Furthermore, the applications of these methodologies are often plagued by the electron-deficient aryl organometallic reagents that are difficult to prepare and of the low reactivity.

As increasingly viable alternatives to traditional cross-coupling reactions, C−H direct arylation reactions have been a very active field of research since such transformations are capable of streamlining organic synthesis and

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minimizing wasteful byproducts.[3−8] Significant advances in direct arylation reactions have been achieved by employing a variety of catalyst systems incorporating Pd,[4] Rh,[5] Ru,[6] Cu,[7] Ni,[8] and Fe.[9] These established methods demonstrated that direct arylation reactions not only offer improved efficiency to the overall processes by using simple arenes in place of organometallics and/or aryl halides but also provide a strategic solution to long-standing challenges associated with the use of problematic organometallics. For example, the elegant studies by Fagnou and Daugulis established the direct arylation of polyfluorobenzenes with aryl halides, eliminating the need for electron-deficient polyfluoroaryl organoboron reagents.[7b,10] The reactivity of acidic C−H bond toward direct arylation is applicable to the syntheses of the nitrogen-containing heterobiaryls in which readily available and cheap electron-deficient nitrogen heterocycles such as pyridine *N*-oxides were used as replacements for unstable and/or unisolable heterocyclic organometallics.[11]

Metal-catalyzed decarboxylative aryl−aryl cross-coupling provides another promising access to (hetero)biaryl compounds, in which aromatic carboxylic acids are used as arylating reagents in place of expensive organometallic reagents in traditional cross-coupling reactions.[12] Owing to ready availability of a wide range of aromatic carboxylic acids, decarboxylative cross-coupling reactions have attracted considerable interest since the pioneering studies by Myers[13] and Goossen[14] were reported. As a result, successes in decarboxylative cross-coupling of aromatic carboxylic acids with aryl halides or olefins have been accomplished by using Pd/Cu,[14a−f] Pd/Ag,[13,15] Pd,[16] and Cu[17] catalysts, and the decarboxylative coupling reactions of α-amino acids with different nucleophiles have been established.[18] Yu[19] and Daugulis[20] have independently developed catalytic methods for carboxyl-directed *ortho*-C-H functionalization, and Miura's seminal work on coupling reaction of benzoic acids with alkynes for construction of fused rings has further highlighted the great potential of benzoic acids to serve as versatile starting materials for syntheses of complex molecules.[21]

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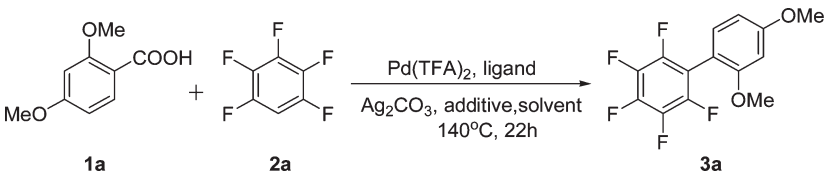
TABLE 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	ligand (equiv)	additive (equiv)	yield[b] (%)
1[c]		MS	20
2	PCy_3 (0.6)	MS	44
3	PCy_3 (0.6)	K_3PO_4 (1.5), MS	70
4		K_3PO_4 (1.5), MS	10
5	PCy_3 (0.4)	K_3PO_4 (1.5), MS	55
6	PCy_3 (0.2)	K_3PO_4 (1.5), MS	13
7	P $^{t\text{-}}Bu_3$ (0.6)	K_3PO_4 (1.5), MS	22
8	$P^{n\text{-}}Bu_3$ (0.6)	K_3PO_4 (1.5), MS	< 5
9	$P^{t\text{-}}Bu_2Me$ (0.6)	K_3PO_4 (1.5), MS	60
10	$P^{i\text{-}}Pr_3$ (0.6)	K_3PO_4 (1.5), MS	53
11	PPh_3 (0.6)	K_3PO_4 (1.5), MS	25
12	X-Phos[d] (0.6)	K_3PO_4 (1.5), MS	28
13	PCy_3 (0.6)	K_3PO_4 (1.5)	66
14	PCy_3 (0.6)	Na_3PO_4 (1.5), MS	63
15	PCy_3 (0.6)	K_2CO_3 (1.5), MS	60
16	PCy_3 (0.6)	Na_2CO_3 (1.5), MS	57
17	PCy_3 (0.6)	K_2HPO_4 (1.5), MS	60
18[e]	PCy_3 (0.45)	K_3PO_4 (1.5), MS	75
19[f]	PCy_3 (0.3)	K_3PO_4 (1.5), MS	44

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv), $Pd(TFA)_2$ (20 mol %), Ag_2CO_3 (3.5 equiv), 3 Å MS (100 mg), 2.0 mL of solvent (7% DMSO/1,4-dioxane), 140 °C, 22 h. [b]Isolated yields. [c]7% DMSO/DMF. [d]2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [e]$Pd(TFA)_2$ (15 mol %). [f]$Pd(TFA)_2$ (10 mol %).

Recently, the reaction that combines decarboxylation of benzoic acids with direct functionalization of C−H bond for synthesis of biaryl has emerged. Such transformations take advantage of both the high efficiency of direct C−H bond functionalization and the wide diversity of carboxylic acids and offer new bond-forming strategies in synthesis. In this context, Crabtree and co-workers have reported for the first time four examples of decarboxylative coupling of 2, 6-dimethoxybenzoic acid with arene donors in low to moderate yields at high temperature (200 °C).[22] Subsequently, Glorius and co-workers have reported palladium catalyzed intramolecular direct arylation of benzoic acids by tandem decarboxylation/C−H activation.[23] Very recently, the intermolecular decarboxyltive C3 arylation of indoles with electron-deficient benzoic acids was achieved by Larrosa,[24] and the intermolecular decarboxylative C−H cross-coupling between oxazoles and thiazoles was reported by Greaney.[25] We have established a versatile Pd/Ag catalyst system for highly regioselective arylation of a wide range of indoles with both electron-rich and -deficient benzoic acids in which the regioselectivity is governed by the nature of benzoic acids, and also realized decarboxylative coupling of aromatic carboxylic acids with nitroethane via combination of decarboxylation and cleavage of sp^3 C−H bond for selective synthesis of (*E*)-β-nitrostyrenes.[26] Despite these advances, the reactions for the direct C−H arylation based on decarboxylation of aromatic carboxylic acids are still scarce. In this full article, we report direct arylation of an array of electron-deficient fluorobenzenes with both electron-rich and -deficient aromatic carboxylic acids as arylating reagents using Pd catalyst supported by tricyclohexylphosphine (PCy_3) ligand, and present the results of a mechanistic investigation on this reaction.[27]

Results and Discussion

Development of the Decarboxylative Cross-Coupling Reaction of Benzoic Acid with Fluorobenzene. The reaction of 2, 4-dimethoxybenzoic acid (**1a**) with pentafluorobenzene (**2a**) was employed as the model for optimization studies (Table 1). Initially, the reaction of **1a** with 3 equiv of **2a** carried out under the previously established conditions for the decarboxylative cross-coupling of benzoic acids with indoles or nitroethane [20 mol % of $Pd(TFA)_2$ (TFA = trifluoroacetate), 3.5 equiv of Ag_2CO_3, 3 Å molecular sieves (MS 100 mg for 0.2 mmol **1a**) in a mixed solvent of DMSO (7% v/v) in DMF at 140 °C] afforded the desired product in 20% yield (Table 1, entry 1).[26] The structure of product **3a** was elucidated by NMR spectra and confirmed by the X-ray crystallographic analysis (Supporting Information). However, the unreactive palladium black was formed rapidly in this reaction, which would result in low conversion. In the

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(27) When we established the optimized conditions of the reaction and finished investigating the scope of aromatic carboxylic acids, a few examples of decarboxylative coupling of 2,6-dimethoxybenzoic acid or four derivatives of 2-nitrobenzoic acid with pentafluorobenzene or 2,3,5,6-tetrafluoroanisole in moderate yields were reported; see: Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564.

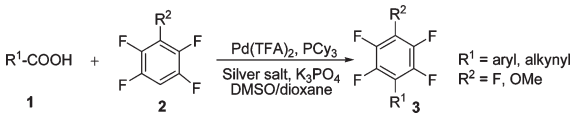
Pd-catalyzed direct arylation of fluorobenzenes with aryl halides, electron-rich trialkylphosphine ligands were required to obtain active catalyst for oxidative addition of aryl halides and cleavage of C−H bond in fluorobenzenes via concerted metalation-deprotonation.[10a,28] In light of this, tricyclohexylphosphine was introduced into the reaction system to lead to the improved yield (Table 1, entry 2). In this case, tricyclohexylphosphine ligand presumably not only exerted a positive effect on Pd-mediated C−H cleavage but also stabilized palladium catalyst against formation of inactive palladium black. The addition of K_3PO_4 (1.5 equiv) led to further improvement of yield (Table 1, entry 3), in agreement with the observation that bases were required for direct functionalization of acidic C−H bond.[10,11] In contrast, the reaction of **1a** with **2a** gave a poor yield in the absence of PCy_3 under otherwise identical conditions (Table 1, entry 4), highlighting the beneficial effect of PCy_3. Reducing the PCy_3/Pd ratio from 3:1 to 2:1 and 1:1 led to a decrease in yield (Table 1, entries 5 and 6).

Screening phosphine ligands revealed that the outcomes of this reaction are sensitive to the structure of phosphine ligands. Compared with PCy_3, both the more hindered P^tBu_3 and the less hindered P^nBu_3 significantly reduced the efficiency of reaction (Table 1, entries 7 and 8). P^tBu_2Me and P^iPr_3 were both slightly less effective than PCy_3 (Table 1, entries 9 and 10). The aryl-substituted phosphines, for example, PPh_3, were essentially ineffective for the enhancement of yield (Table 1, entry 11). Molecular sieves (3 Å) were believed to remove the water generated from the reaction and therefore avoid protodecarboxylation of aromatic carboxylic acid, which was supported by the reaction in the absence of molecular sieves that gave a slightly lower yield than that obtained in the presence of molecular sieves (Table 1, entry 13 vs entry 3). The further investigation of the effect of bases on the reaction outcome showed that K_3PO_4 provided the best result (Table 1, entries 14−17). Interestingly, reducing Pd loading from 20 to 15 mol % increased the yield of the corresponding product, perhaps because a decrease in Pd loading suppressed the homocoupling as well as the aggregation of Pd(0) species into palladium black (Table 1, entry 18). However, when Pd loading was reduced to 10 mol %, only 44% yield was obtained (Table 1, entry 19). Among the palladium sources examined, $Pd(TFA)_2$, which contains the weakest coordination counteranion, proved to be most effective, implying that dissociation of counteranion from the Pd center was probably involved in the reaction process. Other solvents such as DMF, DMSO, NMP, and 1,4-dioxane gave lower yields than the mixed solvents (7% DMSO/1,4-dioxane), and other silver sources such as Ag_2O, AgOTf, AgOAc, and Ag_3PO_4 were less efficient than Ag_2CO_3 (see the Supporting Information).

Scope with Regard to the Aromatic Carboxylic Acids. Establishing the optimized reaction conditions, we explored the scope of this reaction with respect to aromatic carboxylic acids (Table 2). A variety of aromatic carboxylic acids can be used for the direct arylation of polyfluorobenzenes under the optimized conditions. However, in some cases, the optimized reaction conditions need to be adjusted to different carboxylic acids to obtain the best yields. The reason behind

(28) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

TABLE 2. Reaction Scope: Aromatic Carboxylic Acids[a]



Entry	Carboxylic acids	Arene	Product	Yield (%)[b]
1	1a	2a	3a	75
2	1b	2a	3b	50
3[c]	1c	2a	3c	71
4[d]	1d	2a	3d	67
5	1d	2b	3e	67
6[d]	1e	2a	3f	60
7	1e	2b	3g	65
8[d]	1f	2a	3h	67
9[d]	1g	2b	3i	60
10	1h	2a	3j	92
11	1i	2a	3k	86
12[d]	1j	2a	3l	88
13[e]	1k	2a	3m	88
14	1l	2b	3n	62
15	1m	2a	3o	26

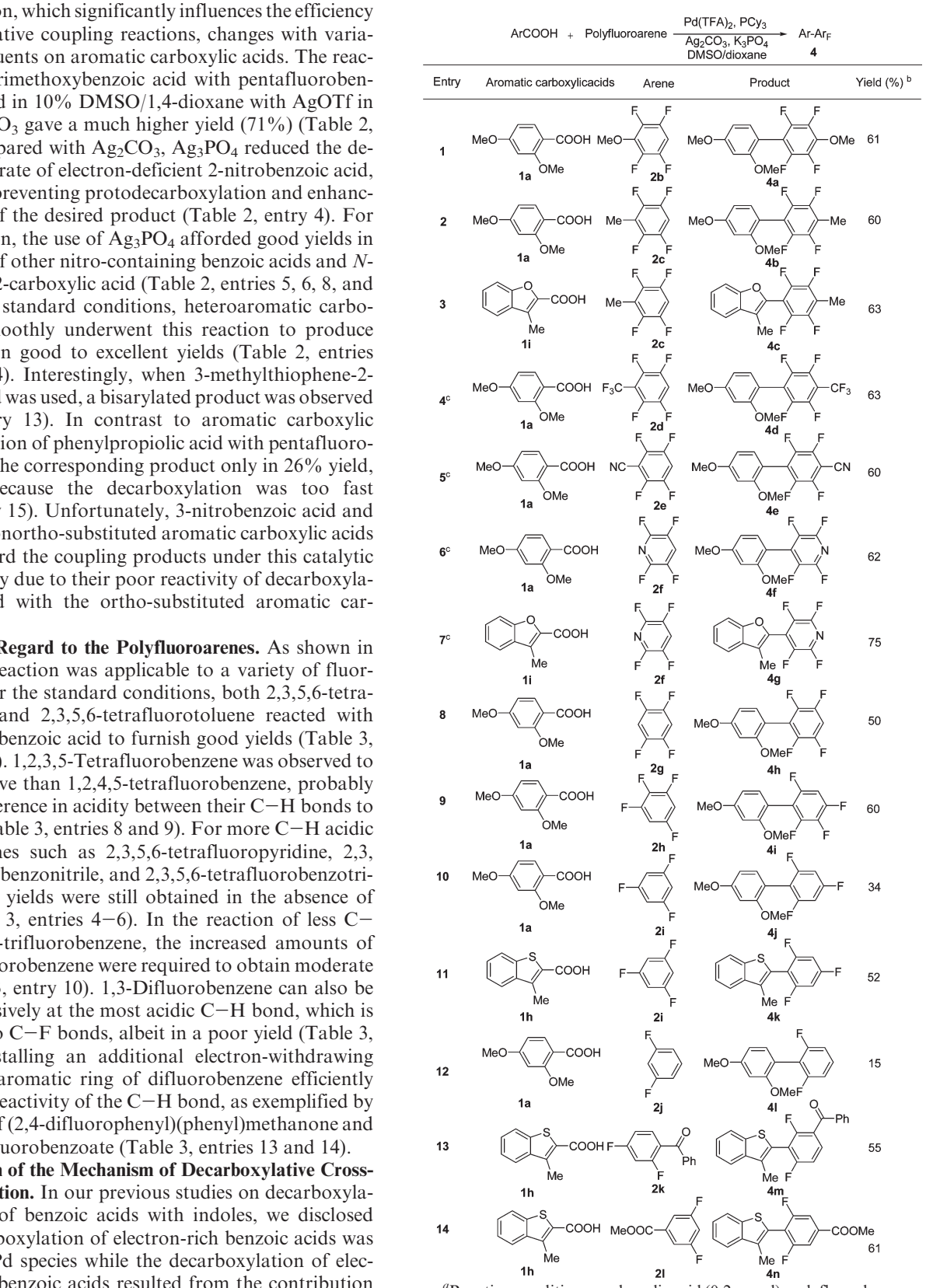
[a]Reaction conditions: carboxylic acid **1** (0.2 mmol), polyfluorobenzene **2** (3.0 equiv), $Pd(TFA)_2$ (15 mol %), PCy_3 (0.45 equiv), Ag_2CO_3 (3.5 equiv), K_3PO_4 (1.5 equiv), 3 Å MS (100 mg), 2.0 mL of solvent, 140 °C, 22 h. See the Supporting Information for details. [b]The yields of **3** were isolated yields. [c]AgOTf (2.5 equiv), K_3PO_4 (2.5 equiv). [d]Ag_3PO_4 (1.5 equiv), K_3PO_4 (2.0 equiv). [e]Pentafluorobenzene (5 equiv), K_3PO_4 (3.0 equiv).

this is that the reactivity of aromatic carboxylic acids toward decarboxylation, which significantly influences the efficiency of decarboxylative coupling reactions, changes with variation of substituents on aromatic carboxylic acids. The reaction of 2,4,5-trimethoxybenzoic acid with pentafluorobenzene conducted in 10% DMSO/1,4-dioxane with AgOTf in place of Ag_2CO_3 gave a much higher yield (71%) (Table 2, entry 3). Compared with Ag_2CO_3, Ag_3PO_4 reduced the decarboxylation rate of electron-deficient 2-nitrobenzoic acid, consequently preventing protodecarboxylation and enhancing the yield of the desired product (Table 2, entry 4). For the same reason, the use of Ag_3PO_4 afforded good yields in the reactions of other nitro-containing benzoic acids and *N*-methylindole-2-carboxylic acid (Table 2, entries 5, 6, 8, and 9). Under the standard conditions, heteroaromatic carboxylic acids smoothly underwent this reaction to produce heterobiaryls in good to excellent yields (Table 2, entries 10, 11, and 14). Interestingly, when 3-methylthiophene-2-carboxylic acid was used, a bisarylated product was observed (Table 2, entry 13). In contrast to aromatic carboxylic acids, the reaction of phenylpropiolic acid with pentafluorobenzene gave the corresponding product only in 26% yield, presumably because the decarboxylation was too fast (Table 2, entry 15). Unfortunately, 3-nitrobenzoic acid and other tested nonortho-substituted aromatic carboxylic acids could not afford the coupling products under this catalytic system, probaly due to their poor reactivity of decarboxylation compared with the ortho-substituted aromatic carboxylic acids.

Scope with Regard to the Polyfluoroarenes. As shown in Table 3, this reaction was applicable to a variety of fluoroarenes. Under the standard conditions, both 2,3,5,6-tetrafluoroanisole and 2,3,5,6-tetrafluorotoluene reacted with 2,4-dimethoxybenzoic acid to furnish good yields (Table 3, entries 1 and 2). 1,2,3,5-Tetrafluorobenzene was observed to be more reactive than 1,2,4,5-tetrafluorobenzene, probably due to the difference in acidity between their C−H bonds to be arylated (Table 3, entries 8 and 9). For more C−H acidic polyfluoroarenes such as 2,3,5,6-tetrafluoropyridine, 2,3,5,6-tetrafluorobenzonitrile, and 2,3,5,6-tetrafluorobenzotrifluoride, good yields were still obtained in the absence of K_3PO_4 (Table 3, entries 4−6). In the reaction of less C−H-acidic 1,3,5-trifluorobenzene, the increased amounts of K_3PO_4 and fluorobenzene were required to obtain moderate yields (Table 3, entry 10). 1,3-Difluorobenzene can also be arylated exclusively at the most acidic C−H bond, which is flanked by two C−F bonds, albeit in a poor yield (Table 3, entry 12). Installing an additional electron-withdrawing group to the aromatic ring of difluorobenzene efficiently enhanced the reactivity of the C−H bond, as exemplified by the reactions of (2,4-difluorophenyl)(phenyl)methanone and methyl 3,5-difluorobenzoate (Table 3, entries 13 and 14).

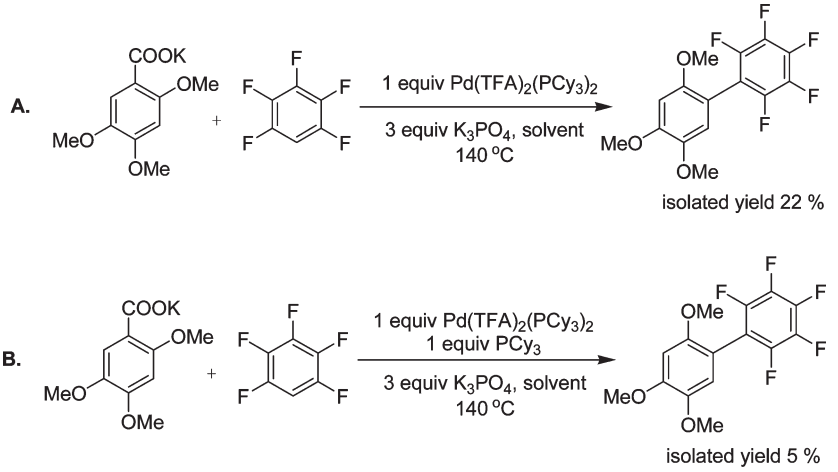
Investigation of the Mechanism of Decarboxylative Cross-Coupling Reaction. In our previous studies on decarboxylative coupling of benzoic acids with indoles, we disclosed that the decarboxylation of electron-rich benzoic acids was catalyzed by Pd species while the decarboxylation of electron-deficient benzoic acids resulted from the contribution of Ag salt.[26a] However, for the Pd/Ag-promoted decarboxylative coupling of aromatic carboxylic acids with polyfluoroarenes, the roles of Pd and Ag in the decarboxylation process remain to be identified because of the presence

TABLE 3. Reaction Scope: Polyfluoroarenes[a]



[a]Reaction conditions: carboxylic acid (0.2 mmol), polyfluorobenzene (3.0−5.0 equiv), $Pd(TFA)_2$ (15 mol %), PCy_3 (0.45 equiv), Ag_2CO_3 (3.5 equiv), K_3PO_4 (1.5 equiv), 3 Å MS (100 mg), 2.0 mL of solvent, 140 °C, 22 h. See the Supporting Information for details. [b]The yields of **4** were isolated yields. [c]In the absence of K_3PO_4.

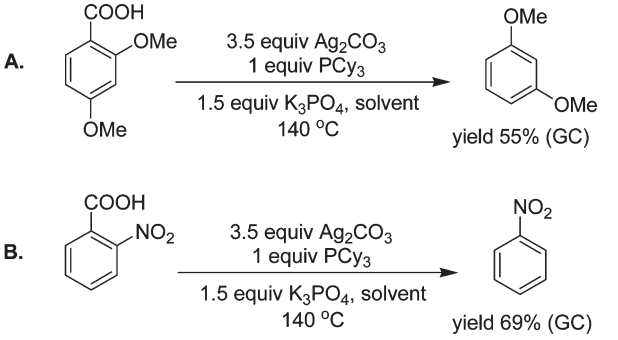
SCHEME 1. Stoichiometric Palladium-Mediated Decarboxylative Arylation



of phosphine ligand in this reaction system and different reaction conditions. Myers,[13c] Fu and Liu[29] reported that electron-donating ligands inhibited the Pd-mediated decarboxylation. Since ^{31}P NMR studies revealed that $Pd(TFA)_2$ combines with PCy_3 with the Pd/PCy_3 ratios of 1:1, 1:2, and 1:3 to initially generate $Pd(TFA)_2(PCy_3)_2$[30] as the only Pd/PCy_3 complex, we examined the reaction of potassium 2,4,5-trimethoxybenzoate with pentafluorobenzene with stoichiometric $Pd(TFA)_2(PCy_3)_2$ in the absence of Ag_2CO_3 and found that this reaction generated the corresponding product in 22% yield (Scheme 1A), which indicated that the Pd complex containing phosphine ligand was capable of mediating decarboxylation. Further addition of additional PCy_3 (1 equiv) to this reaction system reduced the yield of product to about 5% (Scheme 1B), which suggested that the dissociation of PCy_3 from Pd complex was likely involved in the reaction process. For the real catalyst system where the Pd/PCy_3 ratio is 3:1, it seems reasonable to assume that Ag salts served as the scavenger of extra PCy_3 ligand and therefore allowed decarboxylative coupling to occur. However, further investigations complicated the determination of the roles of Pd and Ag in the decarboxylation process. Although no decarboxylative product was detectable in the reaction of 2,4-dimethoxybenzoic acid with 3.5 equiv of Ag_2CO_3 in 7% DMSO/dioxane at 140 °C in the presence of K_3PO_4, the introduction of 1 equiv of PCy_3 led to protodecarboxylation of 2,4-dimethoxybenzoic acid in 55% yield (Scheme 2A), which was presumably due to the formation of soluble Ag/PCy_3 complex. Thus, it is possible that both Pd and Ag participated in the decarboxylation of electron-rich aromatic carboxylic acids.

In the cases of electron-deficient aromatic carboxylic acids, Pd complexes were observed to be ineffective for the decarboxylation, in agreement with Larrosa's observation.[24] The reaction of 2-nitrobenzoic acid with 3.5 equiv of Ag_2CO_3 that was conducted in 7% DMSO/dioxane at 140 °C for 22 h in the presence of K_3PO_4 and PCy_3 generated the protodecarboxylation product in 69% yield (Scheme 2B). These observations showed clearly that only

SCHEME 2. Silver-Promoted Protodecarboxylation



Ag salts were responsible for the decarboxylation of electron-deficient aromatic carboxylic acids.[31]

By analogy to the Pd-catalyzed direct arylation of polyfluorobenzenes with aryl halides[10a] or arylboronic acids[32] that was proposed to proceed through the initial formation of arylpalladium intermediate generated from aryl halides or arylboronic acids, subsequent palladation of polyfluorobenzene, and reductive elimination, we speculated that a similar reaction pathway could operate in the Pd/Ag-mediated decarboxylative coupling of aromatic carboxylic acids with polyfluoroarenes. This hypothesis was supported by the fact that the reaction of 2,4,5-trimethoxyphenylpalladium trifluoroacetate complex **5**[13c] with pentafluorobenzene in the presence of 3 equiv of PCy_3 and 3 equiv of K_3PO_4 gave rise to the arylation of pentafluorobenzene in 49% yield (Scheme 3A). Further experiments showed that 15 mol % of arylpalladium **5** catalyzed the direct arylation of pentafluorobenzene with 2,4-dimethoxybenzoic acid in 65% yield (Scheme 3B), suggesting that the arylpalladium intermediate was likely involved in the catalytic cycle.

To explain the two different decarboxylation processes, two possible reaction pathways were proposed for the Pd/Ag-mediated decarboxylative coupling of aromatic carboxylic acids with polyfluorobenzenes (Scheme 4). The

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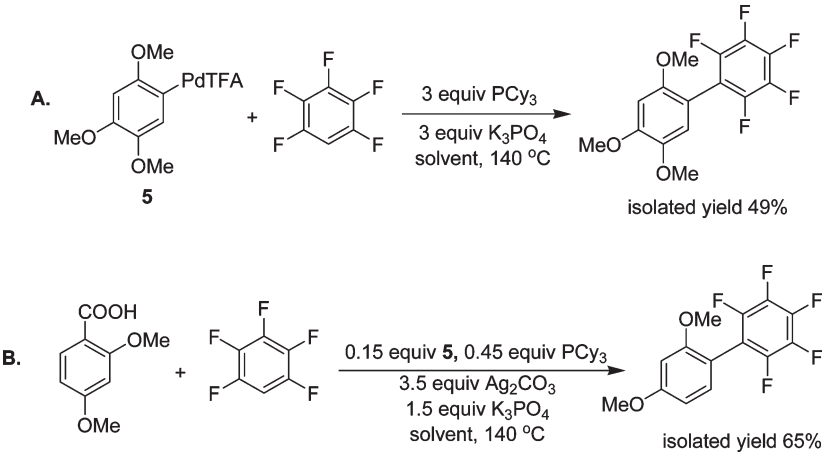
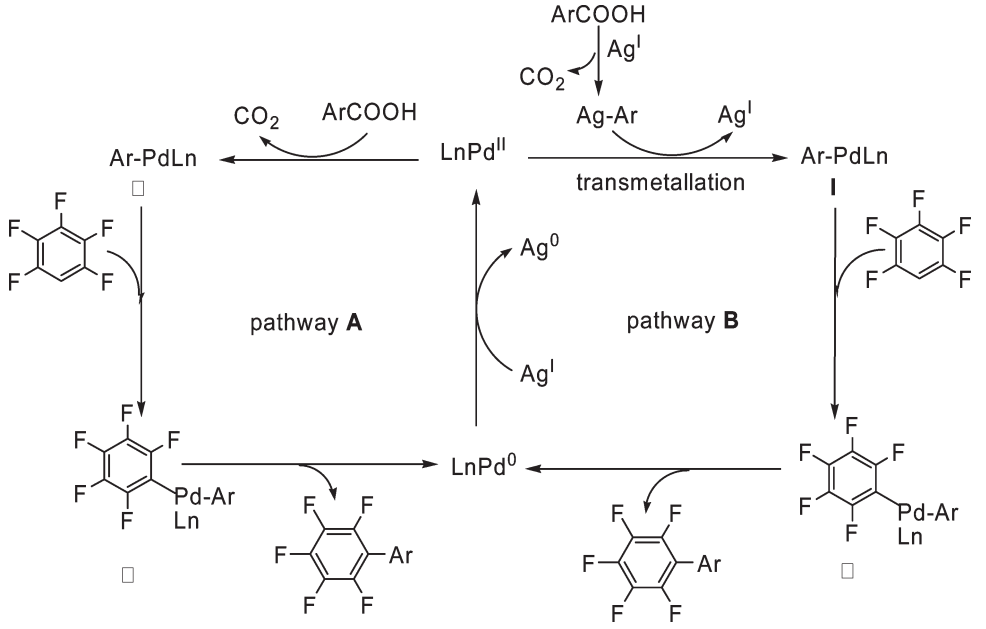
(30) Thirupathi, N.; Amoroso, D.; Bell, A.; Protasiewicz, J. D. *Organometallics* **2007**, *26*, 3157.
(31) (a) Cornella, J.; Sanchez, C.; Banawa, D.; Larrosa, I. *Chem. Commun.* **2009**, 7176. (b) Goossen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P.; Fromm, A. *Chem. Commun.* **2009**, 7173.
(32) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346.

SCHEME 3. Arylpalladium-Promoted Cross-Coupling



SCHEME 4. Proposed Reaction Pathways for the Decarboxylative Arylation of Carboxylic Acids with Polyfluorobenzenes



difference between two pathways lies in the decarboxylation of aromatic carboxylic acids before the formation of arylpalladium intermediates. Pathway A starts with the formation of arylpalladium intermediates via Pd-mediated decarboxylation, whereas pathway B begins by the formation of arylsilver intermediates via Ag-mediated decarboxylation, followed by transmetalation from Ag to Pd to generate arylpalladium intermediates. In their late stages, these two pathways share common elementary steps: palladation of polyfluorobenzene, reductive elimination, and reoxidation of Pd(0) to Pd(II).[23,27,32,33]

By running the reactions of proto- and deutero-2,3,5,6-tetrafluoroanisoles with 2,4-dimethoxybenzoic acid side by side in separate flasks, a kinetic isotope effect of 4.0 was observed (Scheme 5), indicating that the C−H cleavage of polyfluorobenzenes is involved in the rate-determining step. This result provides an explanation for the observation that the deceleration of decarboxylation enhanced the yields of the desired cross-coupling products and efficiently suppressed the protodecarboxylation of aromatic carboxylic acids. The competition experiment was also performed to determine relative reactivities of polyfluorobenzenes. Competition between arylation of pentafluorobenzene and 2,3,5,6-tetrafluoroanisole with 2,4-dimethoxybenzoic acid delivered preferentially the product from pentafluorobenzene (Scheme 6), indicating that the more C−H acidic polyfluorobenzene obtains the higher reactivity.

Conclusions

In the presence of silver salts, $Pd(TFA)_2/PCy_3$ proved to be a versatile catalyst system for the decarboxylative coupling of aromatic carboxylic acids with polyfluoroarenes. This protocol allowed using both electron-deficient and -rich aromatic carboxylic acids as arylating reagents for the direct arylation of a variety of polyfluoroarenes to produce biaryls including some heterobiaryls that were synthesized for the

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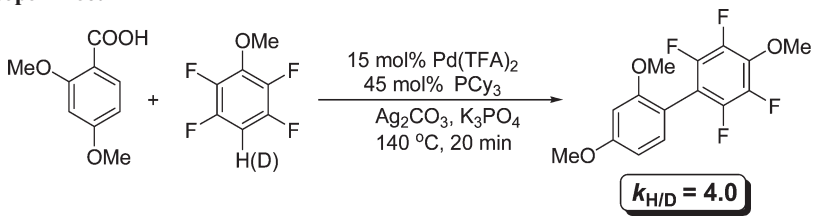
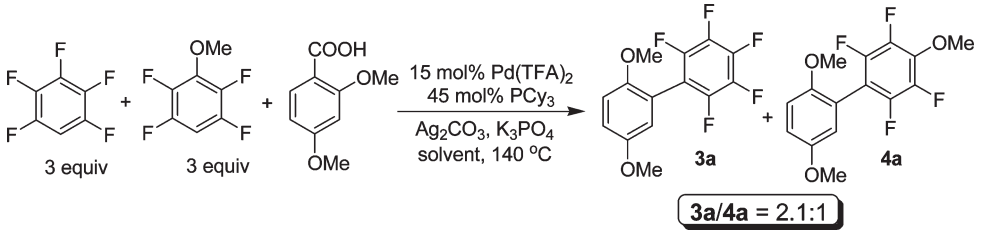
SCHEME 5. Kinetic Isotope Effect



SCHEME 6. Competition between Pentafluorobenzene and 2,3,5,6-Tetrafluoroanisole



first time, providing a complement to the existing methods for the direct arylation of polyfluoroarenes with aryl halides. The choice of silver salts depending on the reactivity of aromatic carboxylic acids was critical to controlling the decarboxylation rate and achieving high-yielding decarboxylative cross-coupling, which can be rationalized by the fact that the rate-determining step involves C−H cleavage step. Mechanistic investigations revealed that both silver salts and the Pd−phosphine complex participated in decarboxylation of electron-rich aromatic carboxylic acids whereas only silver salts resulted in decarboxylation of electron-deficient benzoic acids. We believe that combination of a Pd-catalyzed process with Ag-promoted decarboxylation will continue to lead to the establishment of new types of decarboxylative cross-coupling reactions. Our current efforts are directed toward these challenging but promising targets.

Experimental Section

Typical Procedure for Pd-Catalyzed Cross-Coupling of Fluorobenzene with Carboxylic Acid. In a glovebox, the Schlenk tube equipped with a stir bar was charged with acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), silver salt, base, and 3 Å MS (100 mg). The tube was fitted with a rubber septum and removed out of the glovebox. Solvent (2 mL) was added to the Schlenk tube through the rubber septum using syringes. Then fluorobenzene was added. The rubber septum was replaced with a Teflon screwcap under nitrogen flow. The mixture was stirred and heated for 22 h. After cooling, the reaction mixture was diluted with ether (10 mL) and filtered through a pad of silica gel, followed by washing the pad of the silica gel with the same solvent (20 mL). The filtrate was washed with water (3 × 15 mL) and then with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel to provide the corresponding product.

2,3,4,5,6-Pentafluoro-2′,4′-methoxy-1,1′-biphenyl (3a). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (75% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.80 (s, 3H), 3.87 (s, 3H), 6.59−6.62 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 55.4, 55.6, 98.9, 104.8, 107.6, 112.5 - 112.9 (m), 132.2, 137.3 (dm, J = 250 Hz), 139.8 (dm, J = 252 Hz), 144.6 (dm, J = 246 Hz), 158.3, 162.2; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −140.4 (dd, J = 22.6, 7.9 Hz, 2F), −156.8 (t, J = 20.8 Hz, 1F), −163.5 (ddd, J = 21.6, 21.6, 7.7 Hz, 2F); mp 82−83 °C. Anal. Calcd for $C_{14}H_9F_5O_2$: C, 55.27; H, 2.98. Found: C, 55.38; H, 3.06.

2,3,4,5,6-Pentafluoro-2′-methoxy-4′-methyl-1,1′-biphenyl (3b). Reaction conditions: 2-methoxy-4-methylbenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (10% DMSO/dioxane), 150 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white solid (50% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.42 (s, 3H), 3.79 (s, 3H), 6.84 (s, 1H), 6.87 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 21.7, 55.6, 112.2, 112.6−113.0 (m), 131.4, 137.6 (dm, J = 251 Hz), 140.8 (dm, J = 250 Hz), 141.6, 144.2 (dm, J = 245 Hz), 157.0; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −140.4 (dd, J = 22.6, 8.0 Hz, 2F), −156.6 (t, J = 21 Hz, 1F), −163.4 (ddd, J = 21.5, 21.5, 7.9 Hz, 2F); mp 72−74 °C. Anal. Calcd for $C_{14}H_9F_5O$: C, 58.34; H, 3.15. Found: C, 58.44; H, 3.20.

2,3,4,5,6-Pentafluoro-2′,4′,5′-trimethoxy-1,1′-biphenyl (3c). Reaction conditions: 2,4,5-trimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), AgOTf (0.50 mmol, 2.5 equiv), K_3PO_4 (0.50 mmol, 2.5 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (10% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (71% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.79 (s, 3H), 3.84 (s, 3H), 3.95 (s, 3H), 6.64 (s, 1H), 6.74 (s, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 56.1, 56.5, 56.7, 97.6, 105.9, 112.4−112.8 (m), 114.9, 138.1 (dm, J = 250 Hz), 139.9 (dm, J = 251 Hz), 148.2, 144.6 (dm, J = 245 Hz), 151.2, 151.9; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −140.2 (dd, J = 22.6, 8.0 Hz, 2F), −156.6 (t, J = 20.1 Hz, 1F), −163.3 (ddd, J = 21.7, 21.7, 8 Hz, 2F); mp 113−115 °C.

Anal. Calcd for $C_{15}H_{11}F_5O_3$: C, 53.90; H, 3.32. Found: C, 53.93; H, 3.38.

2,3,4,5,6-Pentafluoro-2′-nitro-1,1′-biphenyl (3d)[27]. Reaction conditions: 2-nitrobenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_3PO_4 (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white-yellow solid (67% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 112.5−112.9 (m), 121.5, 125.4, 130.9, 133.0, 133.7, 137.6 (dm, J = 252 Hz), 140.9 (dm, J = 253 Hz), 144.4 (dm, J = 251 Hz), 148.4; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −141.3 (dd, J = 21.6, 6.7 Hz, 2F), −153.5 (t, J = 20.7 Hz, 1F), −161.6 (ddd, J = 21.7, 21.7, 7 Hz, 2F); mp 83−84 °C. Anal. Calcd for $C_{12}H_4F_5NO_2$: C, 49.84; H, 1.39; N, 4.84. Found: C, 49.85; H, 1.42; N, 4.86.

2,3,5,6-Tetrafluoro-4-methoxy-2′-nitro-1,1′-biphenyl (3e)[27]. Reaction conditions: 2-nitrobenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoroanisole (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white-yellow solid (67% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.14 (s, 3H), 7.45 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 8.19 (d, J = 8 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 62.2 (t, J = 3.8 Hz), 110.5 (t, J = 18.5 Hz), 122.3, 125.3, 130.4, 133.2, 133.4, 138.4−138.7 (m), 140.7 (dm, J = 251 Hz), 143.9 (dm, J = 245 Hz), 148.6; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ-143.3 (dd, J = 21, 7.2 Hz, 2F), −157.7 (dd, J = 21, 7.2 Hz, 2F); mp 116−118 °C. Anal. Calcd for $C_{13}H_7F_4NO_3$: C, 51.84; H, 2.34; N, 4.65. Found: C, 51.78; H, 2.39; N, 4.62.

2,3,4,5,6-Pentafluoro-4′-methyl-2′-nitro-1,1′-biphenyl (3f)[27]. Reaction conditions: 4-methyl-2-nitrobenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_3PO_4 (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (10% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white-yellow solid (60% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.54 (s, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 21.1, 112.5−112.9 (m), 118.5, 125.8, 132.7, 134.3, 137.7 (dm, J = 251 Hz), 141.0 (dm, J = 253 Hz), 141.9, 143.9 (dm, J = 250 Hz),, 148.2; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −141.3 (dd, J = 22, 7 Hz, 2F), −153.9 (t, J = 20.8 Hz, 1F), −161.8 (ddd, J = 22, 22, 7.8 Hz, 2F); mp 71−73 °C. Anal. Calcd for $C_{13}H_6F_5NO_2$: C, 51.50; H, 1.99; N, 4.62. Found: C, 51.53; H, 2.03; N, 4.65.

2,3,5,6-Tetrafluoro-4-methoxy-4′-methyl-2′-nitro-1,1′-biphenyl (3g). Reaction conditions: 4-methyl-2-nitrobenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoroanisole (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white-yellow solid (65% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.52 (s, 3H), 4.13 (s, 3H), 7.32 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 8.00 (s, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 21.1, 62.2 (t, J = 3.8 Hz), 110.6 (t, J = 3.8 Hz), 119.3, 125.7, 132.9, 134.1, 138.2−138.5 (m), 141.0 (dm, J = 245 Hz), 141.3, 143.6 (dm, J = 245 Hz), 148.4; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −143.3 (dd, J = 21.3, 7.8 Hz, 2F), −157.8 (dd, J = 21.3, 7.8 Hz, 2F); mp 88−90 °C. Anal. Calcd for $C_{14}H_9F_4NO_3$: C, 53.34; H, 2.88; N, 4.44. Found: C, 53.29; H, 2.81; N, 4.40.

2,3,4,5,6-Pentafluoro-4′,5′-dimethoxy-2′-nitro-1,1′-biphenyl (3h). Reaction conditions: 4,5-dimethoxy-2-nitrobenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_3PO_4 (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoroanisole (0.60 mmol, 3.0 equiv) in 2 mL of solvent (10% DMSO/dioxane), 150 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white solid (67% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS)δ 3.97 (s, 3H), 4.03 (s, 3H), 6.75 (s, 1H), 7.83 (s, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 56.5, 56.7, 108.5, 113.0−113.8 (m), 115.2, 137.7 (dm, J = 251 Hz), 141.1, 141.2 (dm, J = 253 Hz), 143.5 (dm, J = 245 Hz), 149.9, 153.2; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −141.1 (dd, J = 21.6, 7.5 Hz, 2F), −154.2 (t, J = 20 Hz, 1F), −161.9 (ddd, J = 21.7, 21.7, 7.2 Hz, 2F); mp 125−127 °C. Anal. Calcd for $C_{14}H_8F_5NO_4$: C, 48.15; H, 2.31; N, 4.01. Found: C, 48.08; H, 2.37; N, 3.97.

2,3,5,6-Tetrafluoro-4-methoxy- 4′-fluoro-2′-nitro-1,1′-biphenyl (3i). Reaction conditions: 4-fluoro-2-nitrobenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_3PO_4 (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoroanisole (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white-yellow solid (60% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.15 (s, 3H), 7.45−7.48 (m, 2H), 7.92−7.95 (m, 1H); ^{13}C (100 MHz, $CDCl_3$, TMS) δ 62.2 (t, J = 3.9 Hz), 109.5 (t, J = 18.3 Hz), 113.1, 113.4, 118.3−118.4 (m), 120.7, 120.9, 134.8, 134.9, 138.8−138.9 (m), 141.0 (dm, J = 247 Hz), 144.4 (dm, J = 252 Hz), 149.3 (d, J = 9 Hz), 161.3, 163.8; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −107.0 (s, 1F), −143.1 (dd, J = 20.6, 7.3 Hz, 2F), −157.5 (dd, J = 20.6, 7.3 Hz, 2F); mp 83−85 °C. Anal. Calcd for $C_{13}H_6F_5NO_3$: C, 48.92; H, 1.89, N, 4.39. Found: C, 48.87; H, 1.92; N, 4.38.

3-Methyl-2-(pentafluorophenyl)benzo[*b*]thiophene (3j). Reaction conditions: 3-methylbenzo[*b*]thiophene-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (92% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.34 (s, 3H), 7.42−7.49 (m, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.1 Hz, 1H); ^{13}C NMR(100 MHz, $CDCl_3$, TMS) δ 12.7, 109.2−109.6 (m), 120.2, 122.3, 122.6, 124.4, 125.4, 133.9, 137.5, 137.6 (dm, J = 252 Hz), 142.5 (dm, J = 245 Hz), 144.8 (dm, J = 251 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −138.0 - 138.1 (m, 2F), −152.2 (t, J = 20.5 Hz, 1F), −161.4 to −161.6 (m, 2F); mp 134−136 °C. Anal. Calcd for $C_{15}H_7F_5S$: C, 57.33; H, 2.25. Found: C, 57.30; H, 2.31.

3-Methyl-2-(pentafluorophenyl)benzofuran (3k). Reaction conditions: 3-methylbenzofuran-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and pentafluorobenzene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white

solid (86% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.27 (s, 3H), 7.30−7.34 (m, 1H), 7.30−7.34 (m, 1H), 7.37−7.41 (m, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 8.6, 106.3−106.7 (m), 111.4, 118.4, 119.9, 122.8, 125.5, 129.3, 137.5, 137.6 (dm, J = 252 Hz), 142.5 (dm, J = 245 Hz), 144.8 (dm, J = 251 Hz), 155.3; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −137.8 (dd, J = 22, 7 Hz, 2F), −152.9 (t, J = 20 Hz, 1F), −161.5 to −161.7 (m, 2F); mp 124−126 °C. Anal. Calcd for $C_{15}H_7F_5O$: C, 60.41; H, 2.37. Found: C, 60.31; H, 2.45.

***N*-Methyl-2-(pentafluorophenyl)indole (3l).** Reaction conditions: 1-methylindole-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_3PO_4 (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2 equiv), 3 Å MS (100 mg), and pentafluorobenzene (1.0 mmol, 5.0 equiv) in 2 mL of solvent (10% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (88% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.59 (s, 3H), 6.65 (s, 1H), 7.13−7.18 (m, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 30.7, 105.8, 107.8−108.1 (m), 109.8, 120.2, 121.1, 122.9, 123.7, 127.5, 138.0 (dm, J = 252 Hz), 138.2, 141.5 (dm, J = 254 Hz), 144.9 (dm, J = 252 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −138.7 (dd, J = 22.7, 7.4 Hz, 2F), −152.8 (t, J = 21 Hz, 1F), −161.4 to −161.5 (ddd, J = 22.1, 22.1, 8 Hz, 2F); mp 115−117 °C. Anal. Calcd for $C_{15}H_8F_5N$: C, 60.61; H, 2.71; N, 4.71. Found: C, 60.54; H, 2.76; N, 4.70.

3-Methyl-2,5-(pentafluorophenyl)thiophene (3m). Reaction conditions: 3-methylthiophene-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.60 mmol, 3 equiv), 3 Å MS (100 mg), and pentafluorobenzene (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (88% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.21 (s, 3H), 7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.56, 108.0−108.4 (m), 109.2−109.5 (m), 122.7, 128.7, 132.8 (t, J = 5.5 Hz), 138.2 (dm, J = 252 Hz), 139.3, 140.8 (dm, J = 245 Hz), 144.0 (dm, J = 247 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −138.0 (dd, J = 22.7, 7.5 Hz, 2F), −139.4 to −139.5 (m, 2F), −152.7 (t, J = 21.4 Hz, 1F), −155.0 (t, J = 21 Hz, 1F), −161.4 to −161.5 (m, 2F), −161.7 to −161.9 (m, 2F); mp 61−63 °C. Anal. Calcd for $C_{17}H_4F_{10}S$: C, 47.46; H, 0.94. Found: C, 47.58; H, 1.01.

2-(2,3,5,6-Tetrafluoro-4-methoxyphenyl)-3-methylfuran (3n). Reaction conditions: 3-methyl-2-furoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoroanisole (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 120 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a colorless oil (62% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.04 (s, 3H), 4.13(s, 3H), 6.39 (d, J = 1.5 Hz, 1H), 7.51 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 10.5 (t, J = 2.7 Hz), 62.1 (t, J = 3.8 Hz), 104.8 (t, J = 17.6 Hz), 113.8, 122.1, 136.4, 138.4−138.6 (m), 140.8 (dm, J = 245 Hz), 144.5 (dm, J = 247 Hz), 148.7; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −141.1 (dd, J = 20.4, 7.8 Hz, 2F), −158.2 to −158.3 (m, 2F). Anal. Calcd for $C_{12}H_8F_4O_2$: C, 55.39; H, 3.10. Found: C, 55.31; H, 3.06.

1,2,3,4,5-Pentafluoro-6-(2-phenylethynyl)benzene (3o)[34]**.** Reaction conditions: phenylpropiolic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and pentafluorobenzene (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 120 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (26% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.37−7.44 (m, 3H), 7.57−7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 73.0−73.1 (m), 100.2−100.3 (m), 101.5−101.6 (m), 121.6, 128.5, 129.6, 131.9, 137.7 (dm, J = 250 Hz), 141.4 (dm, J = 255 Hz), 147.1 (dm, J = 245 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −136.3 (dd, J = 18.9, 7.3 Hz, 2 F), −153.4 (t, J = 20.7 Hz, 1 F), −162.1 to −162.2 (m, 2 F); mp 105−107 °C.

2,3,5,6-Tetrafluoro-4-methoxy-2′,4′-methoxyl-1,1′-biphenyl (4a). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoroanisole (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (61% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.80 (s, 3H), 3.86 (s, 3H), 4.10 (s, 3H), 6.58 - 6.61 (m, 2H), 7.14 (d, J = 9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.4, 55.7, 62.1 (t, J = 3.6 Hz), 98.9, 104.8, 108.5, 110.9−111.3 (m), 132.3, 137.3−137.4 (m), 141.0 (dm, J = 245 Hz), 144.7 (dm, J = 244 Hz), 158.4, 161.9; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −142.1 (dd, J = 22.8, 8.4 Hz, 2F), −159.1 (dd, J = 22.8, 8.4 Hz, 2F); mp 75−77 °C. Anal. Calcd for $C_{15}H_{12}F_4O_3$: C, 56.97; H, 3.82. Found: C, 56.91; H, 3.85.

2,3,5,6-Tetrafluoro-4-methyl-2′,4′-methoxy-1,1′-biphenyl (4b). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluorotoluene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (60% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.31 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 6.58−6.61 (m, 2H), 7.16 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 7.6, 55.2, 55.4, 55.7, 98.9, 104.7, 108.9, 114.4−114.9 (m), 132.3, 143.8 (dm, J = 247 Hz), 145.0 (dm, J = 242 Hz), 158.3, 161.9; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −142.7 (dd, J = 22.4, 12.5 Hz, 2F), −145.1 (dd, J = 22.4, 12.3 Hz, 2F); mp 74−76 °C. Anal. Calcd for $C_{15}H_{12}F_4O_2$: C, 60.00; H, 4.03. Found: C, 59.82; H, 4.07.

2-(2,3,5,6-Tetrafluoro-4-methylphenyl)-3-methylbenzofuran (4c). Reaction conditions: 3-methylbenzofuran-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluorotoluene (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (63% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.26 (s, 3H), 2.36 (s, 3H), 7.30 (t, J = 7.4 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 7.8, 8.7, 108.1 - 108.5 (m), 111.4, 117.2−117.7 (m), 119.8, 122.6, 125.2, 129.4, 138.9, 144.1 (dm, J = 245 Hz), 145.3 (dm, J = 242 Hz), 155.1; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −140.5 (dd, J = 21.5, 12 Hz, 2F), −143.3 (dd, J = 21.1, 12 Hz, 2F); mp 102−104 °C. Anal. Calcd for $C_{16}H_{10}F_4O$: C, 65.31; H, 3.43. Found: C, 65.27; H, 3.46.

2,3,5,6-Tetrafluoro-4-trifluoromethy-2′,4′-methoxyl-1,1′-biphenyl (4d). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3

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(0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluorobenzotrifluoride (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (63% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.81 (s, 3H), 3.88 (s, 3H), 6.59−6.63 (m, 2H), 7.16 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.4, 55.7, 98.9, 104.9, 107.3, 107.9−108.2 (m), 119.7, 121.9−122.4 (m), 131.9, 143.7 (dm, J = 255 Hz), 144.7 (dm, J = 253 Hz), 158.1, 162.6; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −56.2 (t, J = 21.5 Hz, 3F), −138.4 to −138.5 (m, 2F), −141.9 to −142.1 (m, 2F); mp 48−50 °C. Anal. Calcd for $C_{15}H_9F_7O_2$: C, 50.86; H, 2.56. Found: C, 50.78; H, 2.60.

2,3,5,6-Tetrafluoro-4-cyano-2′,4′-methoxy-1,1′-biphenyl (4e). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluorobenzonitrile (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (64% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.80 (s, 3H), 3.87 (s, 3H), 6.59−6.63 (m, 2H), 7.15 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.5, 55.7, 92.4, 98.9, 105.1, 107.0, 107.9, 124.7 - 124.9 (m), 131.9, 144.6 (dm, J = 248 Hz), 146.4(dm, J = 255 Hz), 158.1, 162.9; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −133.7 to −133.9 (m, 2F), −136.9 to −137.0 (m, 2F); mp 102−104 °C. Anal. Calcd for $C_{15}H_9F_4NO_2$: C, 57.89; H, 2.91; N, 4.50. Found: C, 57.83; H, 2.97; 4.48.

2,3,5,6-Tetrafluoro-4-(2,4-dimethoxyphenyl)pyridine (4f). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), 3 Å MS (100 mg), and 2,3,5,6-tetrafluoropyridine (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (62% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ3.82 (s, 3H), 3.88 (s, 3H), 6.60−6.63 (m, 2H), 7.19 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.5, 55.7, 99.0, 105.1, 107.3, 130.9−131.1 (m), 131.7, 138.4−138.7 (m), 140.9−141.2 (m), 142.3, 144.7, 158.1, 163.0; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −89.9 to −90.1 (m, 2F), −139.8 to −139.9 (m, 2F); mp 115−117 °C. Anal. Calcd for $C_{13}H_9F_4NO_2$: C, 54.36; H, 3.16; N, 4.88. Found: C, 54.33; H, 3.18; N, 4.82.

2,3,5,6-Tetrafluoro-4-(3-methylbenzofuran-2-yl)pyridine (4g). Reaction conditions: 3-methylbenzofuran-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), 3 Å MS (100 mg) and 2,3,5,6-tetrafluoropyridine (0.60 mmol, 3.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (75% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.34 (s, 3H), 7.33−7.37 (m, 1H), 7.42−7.46 (m, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 9.0, 111.7, 120.3, 120.9, 123.2, 123.5−123.8 (m), 126.5, 129.0, 137.1, 138.9 (dm, J = 252 Hz), 143.9 (dm, J = 244 Hz), 155.5; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −92.2 to −92.3 (m, 2F), −141.8 to −141.9 (m, 2F); mp 128−130 °C. Anal. Calcd for $C_{14}H_7F_4NO$: C, 59.80; H, 2.51; N, 4.98. Found: C, 59.77; H, 2.53; N, 4.94.

2,3,5,6-Tetrafluoro-2′,4′-methoxy-1,1′-biphenyl (4h). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv), 3 Å MS (100 mg), and 1,2,4,5-tetrafluorobenzene (1.0 mmol, 4.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white solid (50% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.80 (s, 3H), 3.87 (s, 3H), 6.59−6.61 (m, 2H), 7.00−7.06 (m, 1H), 7.16 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.5, 55.6, 98.9, 104.2, 104.5, 104.7, 108.7, 118.2−118.6 (m), 132.1, 144.4 (dm, J=243 Hz), 145.8 (dm, J=244 Hz), 158.2, 162.1; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −140.2 (dd, J = 22.7, 12.5 Hz, 2F), −141.0 (dd, J=22.7, 12.5 Hz, 2F); mp 49−50 °C. Anal. Calcd for $C_{14}H_{10}F_4O_2$: C, 58.75; H, 3.52. Found: C, 58.71; H, 3.56.

2,3,4,6-Tetrafluoro-2′,4′-methoxy-1,1′-biphenyl (4i). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.30 mmol, 1.5 equiv), 3 Å MS (100 mg), and 1,2,3,5-tetrafluorobenzene (1.0 mmol, 4.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (2% ether/petroleum ether) as the eluent to afford a white solid (60% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.79 (s, 3H), 3.86 (s, 3H), 6.58−6.61 (m, 2H), 6.78−6.8 (m, 1H), 7.14 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.4, 55.7, 98.9, 100.1 - 100.6 (m), 104.7, 108.8, 112.6, 112.8, 132.2, 137.3 (dm, J = 245 Hz), 149.1 (dm, J = 244 Hz), 150.1 (dm, J = 248 Hz), 154.8 (dm, J = 243 Hz), 153.6, 156.0, 158.3, 161.8; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −115.9 (d, J = 10.7 Hz, 1F), −132.5 to −132.6 (m, 1F), −134.4 (dd, J = 21.6, 5.2 Hz, 1F), −165.8 to −165.9 (m, 1F); mp 42−44 °C. Anal. Calcd for $C_{15}H_9F_7O_2$: $C_{14}H_{10}F_4O_2$: C, 58.75; H, 3.52. Found: C, 58.77; H, 3.55.

2,3,6-Trifluoro-2′,4′-methoxy-1,1′-biphenyl (4j). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv), 3 Å MS (100 mg), and 1,3,5-trifluorobenzene (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (34% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.78 (s, 3H), 3.86 (s, 3H), 6.57−6.59 (m, 2H), 6.70−6.73 (m, 2H), 7.14 (d, J = 9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.4, 55.7, 98.9, 99.8−100.2 (m), 104.5, 109.8, 111.2−111.5 (m), 132.3, 158.3, 160.1 (dm, J = 247 Hz), 161.5, 161.9 (dm, J = 246 Hz), 163.1; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −109.1 (d, J = 5.7 Hz, 2F), −110.1 (t, J = 6.4 Hz, 1F); mp 70−72 °C. Anal. Calcd for $C_{14}H_{11}F_3O_2$: C, 62.69; H, 4.13. Found: C, 62.72; H, 4.16.

2-(2,4,6-Trifluorophenyl)-3-methylbenzo[*b*]thiophene (4k). Reaction conditions: 3-methylbenzo[*b*]thiophene-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv), 3 Å MS (100 mg), and 1,3,5-trifluorobenzene (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (52% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.29 (s, 3H), 6.79−6.83 (m, 2H), 7.37−7.45 (m, 2H), 7.77 (d, J = 7.4 Hz, 1H), 7.86(d, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 12.6 (t, J = 1.2 Hz), 100.3 - 100.9 (m), 108.0−108.2 (m), 122.2, 122.3, 122.6, 124.1, 124.9, 132.8, 139.8, 140.2, 161.0 (dm, J = 250 Hz), 162.5 (dm, J = 250 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −106.4 (d, J = 6.7 Hz, 2F), −106.5 to −106.6 (m, 1F); mp 94−96 °C. Anal. Calcd for $C_{15}H_9F_3S$: C, 64.74; H, 3.26. Found: C, 64.75; H, 3.30.

2, 6-Difluoro-2′,4′-methoxy-1,1′-biphenyl (4l). Reaction conditions: 2,4-dimethoxybenzoic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3

(0.70 mmol, 3.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv), 3 Å MS (100 mg), and 1,3-difluorobenzene (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using petroleum ether as the eluent to afford a white solid (15% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.78 (s, 3H), 3.86 (s, 3H), 6.57−6.60 (m, 2H), 6.91−6.97 (m, 2H), 7.16−7.19 (m, 1H), 7.24−7.30 (m, 1H, overlap with the chemical shift of $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 55.4, 55.7, 98.9, 104.5, 110.7−111.2 (m), 115.1(t, J = 20 Hz), 128.6 (t, J = 10 Hz), 132.2, 158.4, 161.9, 160.7 (dd, J = 246, 7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −112.2 (s, 2F); mp 52−53 °C. Anal. Calcd for $C_{14}H_{12}F_2O_2$: C, 67.20; H, 4.83. Found: C, 67.24; H, 4.88.

(2,4-Difluoro-3-(3-methylbenzo[*b*]thiophen-2-yl)phenyl)-(phenyl)methanone (4m). Reaction conditions: 3-methylbenzo-[*b*]thiophene-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.4 mmol, 2.0 equiv), 3 Å MS (100 mg), and (2,4-difluorophenyl)(phenyl)methanone (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (55% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.33 (s, 3H), 7.15−7.19 (m, 1H), 7.39−7.43 (m, 2H), 7.48−7.51 (m, 2H), 7.60−7.62 (m, 1H), 7.67−7.69 (m, 1H), 7.76−7.78 (m, 1H), 7.84−7.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 12.8, 112.13 (dd, J = 22.9, 3.8 Hz), 112.5, 112.7, 122.2, 122.4, 122.5, 123.7 (dd, J = 16, 3.8 Hz), 124.2, 125.0, 128.6, 129.7, 132.0 (dd, J = 10.6, 4.7 Hz) (m), 133.1, 133.6, 137.3, 139.8, 140.3, 158.4 (dd, J = 257, 6.6 Hz), 162.4 (dd, J = 256, 5.9 Hz), 192.2; ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −103.1 (d, J = 8.5 Hz, 1F), −105.6 (d, J = 9 Hz, 1F); mp 30−31 °C. Anal. Calcd for $C_{22}H_{14}F_2OS$: C, 72.51; H, 3.87. Found: C, 72.47; H, 3.91.

Methyl 3,5-difluoro-4-(3-methylbenzo[*b*]thiophen-2-yl)benzoate (4n). Reaction conditions: 3-methylbenzo[*b*]thiophene-2-carboxylic acid (0.20 mmol), $Pd(TFA)_2$ (0.03 mmol, 0.15 equiv), PCy_3 (0.09 mmol, 0.45 equiv), Ag_2CO_3 (0.70 mmol, 3.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv), 3 Å MS (100 mg), and methyl 3,5-difluorobenzoate (1.0 mmol, 5.0 equiv) in 2 mL of solvent (7% DMSO/dioxane), 140 °C, 22 h. The reaction mixture was purified by column chromatography on silica gel using (5% ether/petroleum ether) as the eluent to afford a white solid (61% yield): ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.31 (s, 3H), 3.98 (s, 3H), 7.40−7.44 (m, 2H), 7.70 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 7.3 Hz, 1H), 7.86 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 12.8, 52.8, 112.7−113.0 (m), 116.4 (t, J = 20 Hz), 122.3, 122.5, 122.6, 124.2, 125.1, 132.6 (t, J = 9.5 Hz), 133.2, 139.8, 140.4, 160.3 (dd, J = 252, 6.3 Hz), 164.7 (t, J = 3.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, TMS) δ −108.0 (s, 2F); mp 92−94 °C. Anal. Calcd for $C_{17}H_{12}F_2O_2S$: C, 64.14; H, 3.80. Found: C, 64.10; H, 3.84.

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Supporting Information Available: Detailed experimental procedures about the studies of the reaction mechanism, spectral data for new compounds, and X-ray crystallography data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.