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Synthesis of Heteroarylated Polyfluorobiphenyls via Palladium-Catalyzed Sequential sp^2 C−H Bonds Functionalizations

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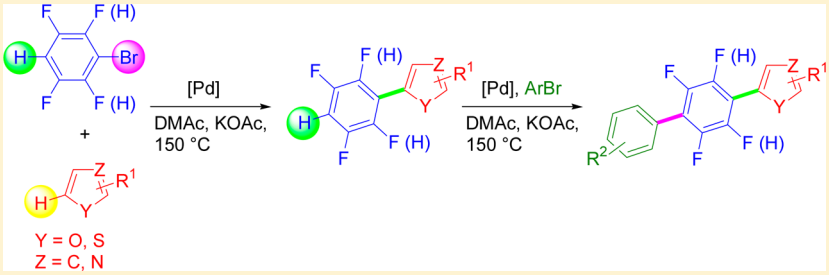
Supporting Information



ABSTRACT: The higher reactivity of C5−H bonds of heteroarenes as compared to C−H bonds of bromopolyfluorobenzenes for palladium-catalyzed direct arylation allows the selective synthesis of the polyfluoroaryl-heteroarenes in moderate to high yields, without C−H bond functionalization of the polyfluorobenzene ring. In most cases, low loading of $Pd(OAc)_2$ catalyst (0.5−1 mol %) was employed. Then, from these heteroarylated polyfluorobenzenes, the palladium-catalyzed C−H bond functionalization of the polyfluorobenzene ring allows the synthesis of heteroarylated polyfluorobiphenyls.

The palladium-catalyzed direct arylation of several (hetero)-aromatics via direct C−H bond activation using aryl halides has brought a synthesis revolution in recent years.[1−3] Such couplings are very attractive to replace classical palladium-catalyzed reactions such as Stille, Suzuki or Negishi couplings as they do not require the preliminary synthesis of one or two organometallic derivatives.[1] Several bioactive compounds contain a (poly)fluorobenzene motif. For example, Atorvastatin and Fluvastatin are used for lowering blood cholesterol, Rufinamide is an anticonvulsant, and Robanacoxib is a nonsteroidal anti-inflammatory drug (Figure 1). Therefore, the discovery of general simple routes to functionalize (poly)fluorobenzenes has potential for medicinal chemistry. More importantly, the tetrafluorobenzene unit also has potential for the production of molecular materials for optics.[4]

Several examples of palladium-catalyzed direct arylation of heteroaromatics with aryl halides have been reported.[1−3] Fagnou and co-workers and other groups have already reported examples of palladium-catalyzed direct arylations of polyfluorobenzenes[5−9] with aryl halides. They observed that C−H bonds bearing two fluoro substituents at the *ortho* position in pentafluorobenzene, tetrafluorobenzenes or even 1,3,5-trifluorobenzene could be arylated with aryl halides (Scheme 1, top).[5a−c] In 2012, Zhang and co-workers have reported the coupling of 3-bromo-1,2,4,5-tetrafluorobenzene with iodoanisole to give the 4-bromo-2,3,5,6-tetrafluoro-4′-methoxybiphenyl using 5 mol % of $Pd(OAc)_2$ associated to 10 mol % of PPh_3 as catalyst (Scheme 1, middle).[10] In the course of this reaction, no cleavage of the C−Br bond of the tetrafluorobenzene derivative was observed.

On the other hand, to our knowledge, the selective direct heteroarylation of tri- or tetra-fluorobromobenzenes without C−H bond activation of the polyfluorobenzene moiety has not been described (Scheme 1, bottom). The discovery of an effective method for the sequential functionalization of C−H and C−Br bonds of bromopolyfluorobenzenes with heteroarenes, especially under low catalyst loading conditions, would be a considerable advantage for simpler access to fluoro-containing poly(hetero)aryls.

Here, we wish to report (i) the efficient palladium-catalyzed heteroarylation of bromopolyfluorobenzenes, without C−H bond activation of the fluorobenzenes moiety, with a wide variety of heteroarenes using low loadings of a phosphine-free palladium catalyst; (ii) the subsequent reactivity of these formed heteroarylated polyfluorobiphenyls for palladium-catalyzed C−H bond functionalization at the polyfluorobenzene ring to produce heteroarylated polyfluorobiphenyls.

As the free energies of activation for direct arylation via concerted metalation deprotonation (CMD)[11,12] pathway calculated by Fagnou and co-workers for 1,3-difluorobenzene or pentafluorobenzene are quite similar to those of furan, thiophene and thiazole, the outcome of the reaction of bromopolyfluorobenzenes with heteroarenes in the presence of palladium catalysts was quite unpredictable and needed to be investigated (Figure 2).

2-Methyl-2-thiophen-2-yl-[1,3]dioxolane and 3-bromo-1,2,4,5-tetrafluorobenzene were employed as model substrates

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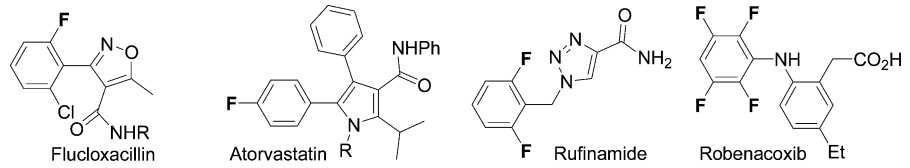
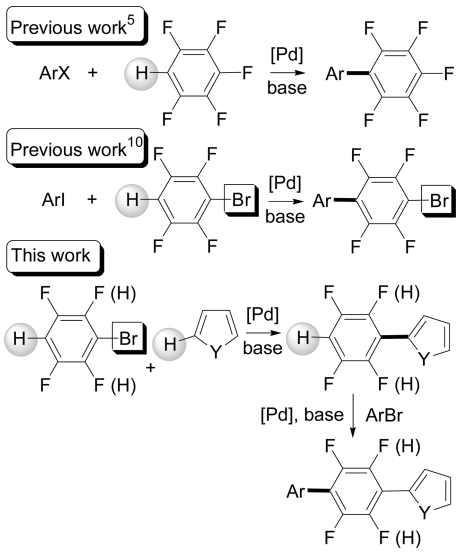


Figure 1. Examples of bioactive fluorobenzene derivatives.

Scheme 1. Palladium-Catalyzed Direct Arylation Using Polyfluorobenzene Derivatives



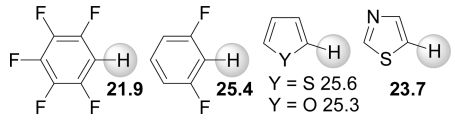
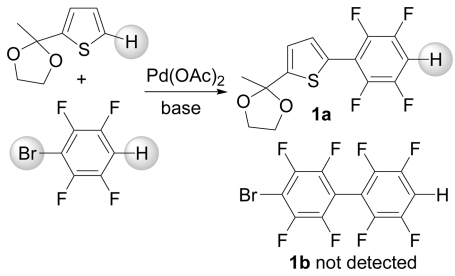


Figure 2. Free energy of activation ($\Delta G^{\ddagger}_{298K}$, kcal mol^{-1}) for direct arylation via the CMD pathway involving an acetate ligand with the [Pd(C_6H_5)(PMe_3)(OAc)] catalyst.[11]

for our study (Scheme 2, Table 1). We initially examined the influence of the nature of the base on aryl bromide conversion

Scheme 2. Coupling of 3-Bromo-1,2,4,5-tetrafluorobenzene with 2-Methyl-2-thiophen-2-yl-[1,3]dioxolane



for this reaction using DMAc as the solvent and 0.5 mol % $Pd(OAc)_2$ catalyst. We had previously observed that these reaction conditions allowed the coupling of several heteroaromatics with aryl bromides.[2f] K_2CO_3 or Cs_2CO_3 gave low conversion of 3-bromo-1,2,4,5-tetrafluorobenzene (Table 1, entries 1 and 2). On the other hand, in the presence of acetate salts, NaOAc, KOAc or CsOAc as the base, high conversions of 3-bromo-1,2,4,5-tetrafluorobenzene were observed, and the

Table 1. Influence of Reaction Conditions on the 5-Arylation of 2-Methyl-2-thiophen-2-yl-[1,3]dioxolane with 3-Bromo-1,2,4,5-tetrafluorobenzene (Scheme 2)[a]

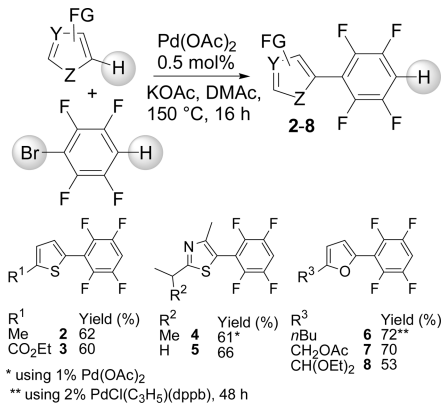
entry	solvent	base	temp (°C)	conv (%)	yield in **1a** (%)
1	DMAc	K_2CO_3	150	10	
2	DMAc	Cs_2CO_3	150	2	
3	DMAc	NaOAc	150	96	65
4	DMAc	KOAc	150	84	74
5	DMAc	CsOAc	150	98	60
6	DMF	KOAc	150	98	40[b]

[a]Conditions: $Pd(OAc)_2$ (0.005 equiv), 3-bromo-1,2,4,5-tetrafluorobenzene (1 equiv), 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (1.5 equiv), base (2 equiv), 16 h, conversion of 3-bromo-1,2,4,5-tetrafluorobenzene, isolated yields. [b]Formation of unidentified side-products was also observed.

coupling product **1a**, retaining the C−H bond of fluorinated aryl group, was isolated in 60−74% yields (Table 1, entries 3−5). In all cases, no formation of product **1b** was detected. Thus these experiments show that the activation of the thienyl C5−H bond is easier than that of the C6−H bond of 3-bromo-1,2,4,5-tetrafluorobenzene. The good performance of acetate as the base/ligand is consistent with the CMD pathway.[12]

Then, 3-bromo-1,2,4,5-tetrafluorobenzene was coupled with a set of heteroarenes in the presence of 0.5−1 mol % $Pd(OAc)_2$, KOAc as the base in DMAc (Scheme 3). Selective

Scheme 3. Heteroarylation of 3-Bromo-1,2,4,5-tetrafluorobenzene



5-arylations of the heteroarenes were observed using 2-methylthiophene and ethyl thiophene-2-carboxylate to give **2** and **3** in 62 and 60% yields, respectively. Good yields were also obtained for the coupling of 2-isopropyl-4-methylthiazole or 2-ethyl-4-methylthiazole with 3-bromo-1,2,4,5-tetrafluorobenzene to give **4** and **5** in 61 and 66% yield, respectively. It should be noted that 2-*n*-butylfuran could also be employed to give **6** in 72% yield. However, 2 mol % of the more stable and more electron-rich catalyst $PdCl(C_3H_5)(dppb)$[13b] had to be employed to obtain a high conversion of the aryl bromide.

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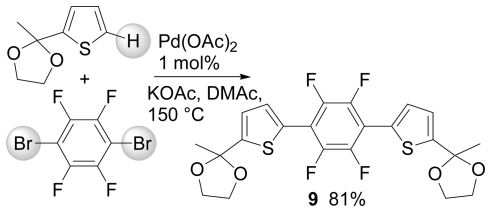
On the other hand, quite good yields in **7** and **8** were obtained from 2-furylmethyl acetate or 2-diethoxymethylfuran using 0.5 mol % $Pd(OAc)_2$ catalyst. In all cases, no formation of **1b** was detected by GC−MS analysis of the crude mixture.

The diheteroarylation of 1,4-dibromo-2,3,5,6-tetrafluorobenzene using 2-methyl-2-thiophen-2-yl-[1,3]dioxolane as the coupling partner was then examined (Scheme 4). The desired

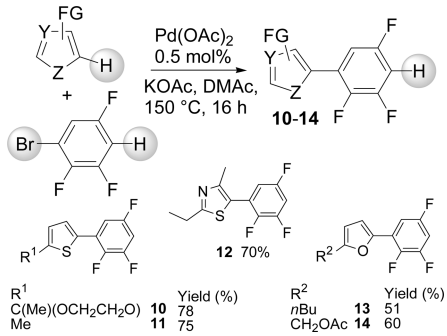
Scheme 4. Diheteroarylation of 1,4-Dibromo-2,3,5,6-tetrafluorobenzene



product **9** was obtained in 81% yield using 1 mol % $Pd(OAc)_2$ catalyst. This method gives a simple access to compounds displaying useful *n*-channel semiconductor properties.[4e]

The reactivity of 1-bromo-2,3,5-trifluorobenzene was then evaluated for C2 heteroarylation (Scheme 5). This reagent was

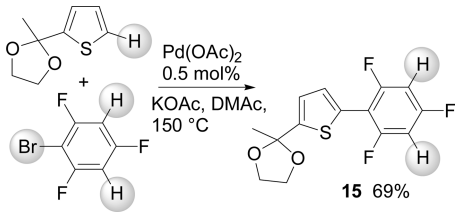
Scheme 5. Heteroarylation of 1-Bromo-2,3,5-trifluorobenzene



successfully coupled with 2-methyl-2-thiophen-2-yl-[1,3]-dioxolane, 2-methylthiophene or 2-ethyl-4-methylthiazole to give the desired products **10**−**12** in 70−78% yields. Slower reactions and lower yields were observed in the presence of 2-*n*-butylfuran or acetic acid furan-2-ylmethyl ester as coupling partners to give **13** and **14** in 51 and 60% yields, respectively.

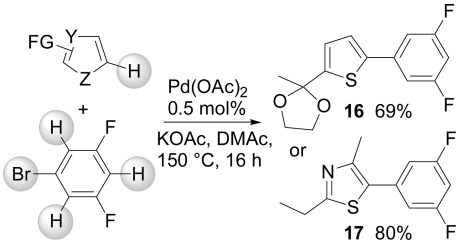
The coupling of 2-bromo-1,3,5-trifluorobenzene with 2-methyl-2-thiophen-2-yl-[1,3]dioxolane was then studied (Scheme 6). In the presence of 0.5 mol % $Pd(OAc)_2$, **15** was obtained in 69% yield. Again, under these reaction conditions, the two C−H bonds of this trifluorobenzene derivative were found to be unreactive.

Scheme 6. Heteroarylation of 2-Bromo-1,3,5-trifluorobenzene



Finally, we examined the reactivity of 1-bromo-3,5-difluorobenzene (Scheme 7). The direct coupling of this

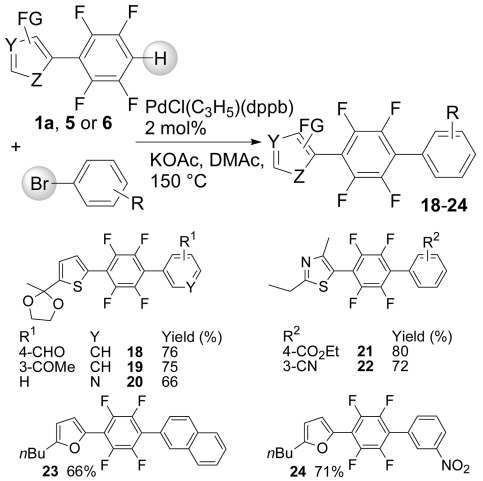
Scheme 7. Heteroarylation of 1-Bromo-3,5-difluorobenzene



substrate with 2-phenylimidazolopyrimidine has already been reported using 8 mol % $Pd(OAc)_2$ associated to 16 mol % PPh_3 as catalyst.[13] Using again 0.5 mol % $Pd(OAc)_2$ and KOAc in DMAc, the desired coupling products **16** and **17** were obtained in 69 and 80% yields from 2-methyl-2-thiophen-2-yl-[1,3]-dioxolane and 2-ethyl-4-methylthiazole as the coupling partners.

Then, the reactivity of the polyfluorobenzene moiety of some of the previously obtained heteroarylated polyfluorobenzene derivatives was evaluated for arylation via C−H bond activation (Scheme 8). 2-Methyl-2-[5-(2,3,5,6-tetrafluorophenyl)-thio-

Scheme 8. 4-Arylation of 1-Heteroaryl-2,3,5,6-tetrafluorobenzenes



phen-2-yl]-[1,3]dioxolane **1a** in the presence of 4-bromobenzaldehyde and 2 mol % $PdCl(C_3H_5)(dppb)$ catalyst gave the desired coupling product **18** in 76% yield. It should be noted that the use of 0.5 mol % $Pd(OAc)_2$ catalyst for this reaction led to a very low yield in **18**. A similar reactivity was observed with 3-bromoacetophenone or 3-bromopyridine to give **19** and **20** in 75 and 66% yields. Then, 2-ethyl-4-methyl-5-(2,3,5,6-tetrafluorophenyl)-thiazole **5** was reacted with ethyl 4-bromobenzoate and 3-bromobenzonitrile. The desired products **21** and **22** were isolated in 80 and 72% yields. Finally, **23** and **24** were obtained in 66 and 71% yields from 2-*n*-butyl-5-(2,3,5,6-tetrafluorophenyl)-furan **6** and 2-bromonaphthalene or 3-bromonitrobenzene as the coupling partners. This coupling arylation of fluorinated arene C−H bonds following the cross-coupling of heterocycles C−H bonds offers a unique access to a variety of heteroaryl−polyfluoroaryl−aryl derivatives.

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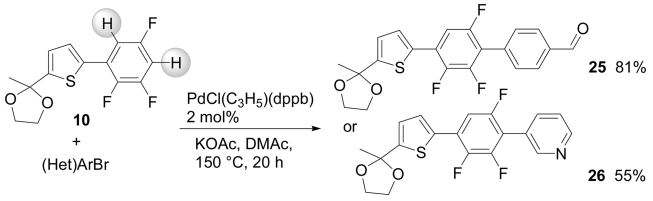
For the couplings with 1-thiazolyl-2,3,5-trifluorobenzene **10**, both positions C4 and C6 on the benzene moiety might have been arylated (Scheme 9). However, with both 4-bromoben-

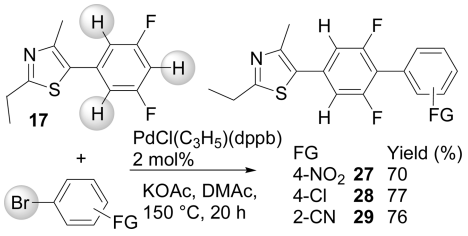
Scheme 9. Regioselective 4-Arylation of 1-Thienyl-2,3,5-trifluorobenzene



zaldehyde and 3-bromopyridine only the arylation at C4 to give **25** and **26** in 81 and 55% yields was observed. This is certainly due to the higher acidity of C4 position.

So far, very few examples of palladium-catalyzed direct arylations at C2 of 1,3-difluorobenzene derivatives have been reported.[5a] However, we found that the catalytic arylation of the difluorobenzene ring of **17** also proceeded nicely with various aryl bromides to give compounds **27**–**29** in good yields (Scheme 10). In all cases, a regioselective arylation at the C–H

Scheme 10. Regioselective 4-Arylation of 1-Thiazolyl-3,5-difluorobenzene



adjacent to the two C–F was observed. It should be noted that from 4-chlorobromobenzene, no cleavage of the C–Cl bond was observed to give **28** in 77% yield allowing further transformations.

In summary, we have demonstrated that C–H bonds of several heteroarenes are more reactive than the C–H bonds of bromo di-, tri- and tetra-fluorobenzenes toward palladium-catalyzed direct arylation. The selective access to new heteroarylated polyfluorobenzenes from bromopolyfluorobenzenes and heteroarenes using only 0.5 mol % of $Pd(OAc)_2$ as the catalyst precursor is reported. The acidity of the C–H bonds adjacent to two ortho C–F bonds of arenes has been profitably used for their further palladium-catalyzed functionalization. This strategy allows straightforward synthesis of heteroarylated polyfluorobiphenyls in good yields via two sequential successive catalytic direct arylations.

EXPERIMENTAL SECTION

General Procedure for Palladium-Catalyzed Direct Arylations of Bromopolyfluorobenzenes. The reaction of the aryl bromide (1 mmol), heteroarene (1.5 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 16 h in DMAc (4 mL) in the presence of $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) or (2.24 mg, 0.01 mmol) (see schemes) under argon affords the coupling products **1**–**8** and **10**–**17** after evaporation of the solvent and purification on silica gel. Eluent pentane:diethylether 9:1 for compounds **1**–**5**, **7**, **8**, **10**, **12**–**17**; pentane:diethylether 4:1 for compound **6**; pentane for compound **11**.

2-Methyl-2-[5-(2,3,5,6-tetrafluorophenyl)-thiophen-2-yl]-[1,3]dioxolane (1a). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (0.340 g, 2 mmol) afford **1a** in 74% (0.235 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 3.8 Hz, 1H), 7.10 (d, J = 3.8 Hz, 1H), 6.98 (tt, J = 9.5, 7.4 Hz, 1H), 4.12–3.97 (m, 4H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (t, J = 3.6 Hz), 146.1 (dm, J = 247.0 Hz), 143.4 (dm, J = 249.8 Hz), 130.5 (t, J = 6.0 Hz), 127.2 (m), 124.3, 115.1 (m), 107.1, 104.0 (t, J = 22.9 Hz), 65.1, 27.6. Elemental analysis calcd (%) for $C_{14}H_{10}F_4O_2S$ (318.29): C 52.83, H 3.17. Found: C 53.02, H 3.30.

2-Methyl-5-(2,3,5,6-tetrafluorophenyl)-thiophene (2). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afford **2** in 62% (0.152 g) yield as an amorphous white solid: mp 43–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 3.8 Hz, 1H), 6.95 (tt, J = 9.5, 7.4 Hz, 1H), 6.84 (d, J = 3.8 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2 (dm, J = 246.8 Hz), 143.4 (dm, J = 249.8 Hz), 143.3 (t, J = 4.0 Hz), 130.6 (t, J = 6.0 Hz), 125.7, 125.2 (m), 115.4 (m), 103.4 (t, J = 22.9 Hz), 15.1. Elemental analysis calcd (%) for $C_{11}H_6F_4S$ (246.22): C 53.66, H 2.46. Found: C 53.50, H 2.59.

Ethyl 5-(2,3,5,6-tetrafluorophenyl)-thiophene-2-carboxylate (3). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and ethyl thiophene-2-carboxylate (0.312 g, 2 mmol) afford **3** in 60% (0.182 g) yield as an amorphous yellow solid: mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 3.8 Hz, 1H), 7.56 (d, J = 3.8 Hz, 1H), 7.06 (tt, J = 9.5, 7.4 Hz, 1H), 4.40 (q, J = 7.3 Hz, 2H), 1.40 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 146.4 (dm, J = 246.8 Hz), 143.6 (dm, J = 249.8 Hz), 136.0 (t, J = 4.0 Hz), 133.8 (m), 132.9, 114.3 (m), 130.6 (t, J = 5.9 Hz), 105.3 (t, J = 22.9 Hz), 61.5, 14.3. Elemental analysis calcd (%) for $C_{13}H_8F_4O_2S$ (304.26): C 51.32, H 2.65. Found: C 51.49, H 2.36.

2-Isopropyl-4-methyl-5-(2,3,5,6-tetrafluorophenyl)-thiazole (4). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.282 g, 2 mmol) afford **4** in 61% (0.176 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (tt, J = 9.5, 7.4 Hz, 1H), 3.32 (sept., J = 7.5 Hz, 1H), 2.32 (s, 3H), 1.43 (d, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 152.5, 146.3 (dm, J = 246.8 Hz), 143.7 (dm, J = 249.8 Hz), 113.6, 113.0 (m), 106.1 (tm, J = 22.7 Hz), 33.4, 23.0, 16.1. Elemental analysis calcd (%) for $C_{13}H_{11}F_4NS$ (289.29): C 53.97, H 3.83. Found: C 53.80, H 3.58.

2-Ethyl-4-methyl-5-(2,3,5,6-tetrafluorophenyl)-thiazole (5). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) afford **5** in 66% (0.181 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (tt, J = 9.5, 7.4 Hz, 1H), 3.05 (q, J = 7.5 Hz, 2H), 2.31 (s, 3H), 1.42 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 152.5, 146.3 (dm, J = 246.8 Hz), 143.7 (dm, J = 249.8 Hz), 114.0, 112.8 (m), 106.2 (tm, J = 22.7 Hz), 26.9, 16.0, 14.0. Elemental analysis calcd (%) for $C_{12}H_9F_4NS$ (275.27): C 52.36, H 3.30. Found: C 52.48, H 3.17.

2-*n*-Butyl-5-(2,3,5,6-tetrafluorophenyl)-furan (6). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and 2-*n*-butylfuran (0.258 g, 2 mmol) afford **6** in 72% (0.196 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (tt, J = 9.5, 7.4 Hz, 1H), 6.86 (d, J = 3.1 Hz, 1H), 6.17 (d, J = 3.1 Hz, 1H), 2.72 (t, J = 7.3 Hz, 2H), 1.69 (quint., J = 7.3 Hz, 2H), 1.42 (sext., J = 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 146.3 (dm, J = 246.8 Hz), 143.7 (dm, J = 249.8 Hz), 140.0 (m), 115.0 (t, J = 6.5 H 112.0 (m), 107.0, 103.2 (t, J = 22.7 Hz), 29.9, 27.8, 22.2, 13.8. Elemental analysis calcd (%) for $C_{14}H_{12}F_4O$ (272.24): C 61.77, H 4.44. Found: C 61.78, H 4.59.

Acetic acid 5-(2,3,5,6-tetrafluorophenyl)-furan-2-ylmethyl ester (7). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and acetic acid furan-2-ylmethyl ester (0.280 g, 2 mmol) afford **7** in 70% (0.201 g) yield as an amorphous yellow solid: mp 55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (tt, J = 9.5, 7.4 Hz, 1H), 6.89 (d, J = 3.1 Hz, 1H), 6.58 (d, J = 3.1 Hz, 1H), 5.13 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 151.0, 146.4 (dm, J = 246.8 Hz), 143.0 (dm, J = 249.8 Hz), 142.7 (t, J = 3.0 Hz), 114.8 (t, J = 6.3 Hz), 112.2, 111.4 (m), 104.4 (t, J = 22.7 Hz), 57.9, 20.8. Elemental analysis

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calcd (%) for $C_{13}H_8F_4O_3$ (288.19): C 54.18, H 2.80. Found: C 54.25, H 2.99.

2-Diethoxymethyl-5-(2,3,5,6-tetrafluorophenyl)-furan (8). 3-Bromo-1,2,4,5-tetrafluorobenzene (0.229 g, 1 mmol) and 2-diethoxymethylfuran (0.340 g, 2 mmol) afford **8** in 53% (0.168 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (tt, J = 9.5, 7.4 Hz, 1H), 6.89 (d, J = 3.1 Hz, 1H), 6.59 (d, J = 3.1 Hz, 1H), 5.61 (s, 1H), 3.75−3.60 (m, 4H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 146.4 (dm, J = 246.8 Hz), 142.9 (dm, J = 249.8 Hz), 141.8 (m), 114.5 (t, J = 6.3 Hz), 111.4 (m), 109.7, 104.1 (t, J = 22.7 Hz), 96.2, 61.6, 15.1. Elemental analysis calcd (%) for $C_{15}H_{14}F_4O_3$ (318.26): C 56.61, H 4.43. Found: C 56.80, H 4.32.

1,4-Di(2-methyl-2-thiophen-2-yl-[1,3]dioxolane)-2,3,5,6-tetrafluorobenzene (9). 1,4-Dibromo-2,3,5,6-tetrafluorobenzene (0.308 g, 1 mmol), 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (0.680 g, 4 mmol) and KOAc (0.392 g, 4 mmol) at 150 °C during 16 h in DMAc (4 mL) in the presence of $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) afford **9** in 81% (0.394 g) yield after evaporation of the solvent and crystallization in dichloromethane/diethyl ether as an amorphous yellow solid: mp 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 3.6 Hz, 2H), 7.11 (d, J = 3.6 Hz, 2H), 4.15−3.95 (m, 8H), 1.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 143.8 (dm, J = 247.0 Hz), 130.3, 127.4, 124.4, 112.4 (m), 107.1, 65.1, 27.6. Elemental analysis calcd (%) for $C_{22}H_{18}F_4O_4S_2$ (486.50): C 54.31, H 3.73. Found: C 54.50, H 3.64.

2-Methyl-2-[5-(2,3,5-trifluorophenyl)-thiophen-2-yl]-[1,3]-dioxolane (10). 1-Bromo-2,3,5-trifluorobenzene (0.211 g, 1 mmol) and 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (0.340 g, 2 mmol) afford **10** in 78% (0.234 g) yield as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 3.8 Hz, 1H), 7.10−7.08 (m, 1H), 7.05 (d, J = 3.8 Hz, 1H), 6.88−6.77 (m, 1H), 4.12−3.97 (m, 4H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (dd, J = 244.8, 11.1 Hz), 151.0 (dt, J = 250.9, 13.6 Hz), 149.3 (d, J = 3.5 Hz), 144.0 (dd, J = 248.0, 11.1 Hz), 134.4 (m), 127.5 (d, J = 7.1 Hz), 124.9, 124.7 (t, J = 11.2 Hz), 109.3 (d, J = 25.1 Hz), 107.0, 103.7 (dd, J = 27.7, 21.4 Hz), 65.0, 27.5. Elemental analysis calcd (%) for $C_{14}H_{11}F_3O_2S$ (300.30): C 55.99, H 3.69. Found: C 56.19, H 3.48.

2-Methyl-5-(2,3,5-trifluorophenyl)-thiophene (11). 1-Bromo-2,3,5-trifluorobenzene (0.211 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) afford **11** in 75% (0.171 g) yield as an amorphous yellow solid: mp 43−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 3.8 Hz, 1H), 7.06−7.00 (m, 1H), 6.83−6.72 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (dd, J = 244.8, 11.1 Hz), 151.0 (dt, J = 250.9, 13.6 Hz), 144.0 (dd, J = 248.0, 11.1 Hz), 142.0 (d, J = 4.1 Hz), 132.6 (m), 127.7 (d, J = 7.1 Hz), 126.3, 125.0 (t, J = 11.2 Hz), 109.0 (d, J = 25.1 Hz), 103.1 (dd, J = 27.7, 21.4 Hz), 15.2. Elemental analysis calcd (%) for $C_{11}H_7F_3S$ (228.23): C 57.89, H 3.09. Found: C 57.90, H 3.30.

2-Ethyl-4-methyl-5-(2,3,5-trifluorophenyl)-thiazole (12). 1-Bromo-2,3,5-trifluorobenzene (0.211 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) afford **12** in 70% (0.180 g) yield as an amorphous yellow solid: mp 44−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00−6.90 (m, 1H), 6.90−6.82 (m, 1H), 3.03 (q, J = 7.3 Hz, 2H), 2.37 (s, 3H), 1.40 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 157.2 (dd, J = 244.8, 11.1 Hz), 150.7 (dt, J = 250.9, 13.6 Hz), 150.5, 144.4 (dd, J = 248.0, 11.1 Hz), 122.9 (m), 121.2, 113.1 (d, J = 24.5 Hz), 105.1 (dd, J = 27.7, 21.4 Hz), 26.9, 16.1, 14.1. Elemental analysis calcd (%) for $C_{12}H_{10}F_3NS$ (257.28): C 56.02, H 3.92. Found: C 56.17, H 4.08.

2-*n*-Butyl-5-(2,3,5-trifluorophenyl)-furan (13). 1-Bromo-2,3,5-trifluorobenzene (0.211 g, 1 mmol) and 2-*n*-butylfuran (0.258 g, 2 mmol) afford **13** in 51% (0.129 g) yield as a yellow oil: ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.35−7.30 (m, 1H), 7.15−7.05 (m, 1H), 6.88 (d, J = 3.1 Hz, 1H), 6.30 (d, J = 3.1 Hz, 1H), 2.74 (t, J = 7.3 Hz, 2H), 1.68 (quint., J = 7.3 Hz, 2H), 1.42 (sext., J = 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8 (dd, J = 244.8, 11.1 Hz), 157.6, 150.7 (dt, J = 250.9, 13.6 Hz), 144.4 (m), 143.0 (dm, J = 247.8, Hz), 121.7 (t, J = 10.6 Hz), 112.9 (d, J = 12.1 Hz), 107.7, 106.5 (d, J = 26.2 Hz), 102.6 (dd, J = 27.9, 21.4 Hz), 30.1, 27.7, 22.2, 13.8. Elemental analysis calcd (%) for $C_{14}H_{13}F_3O$ (254.25): C 66.14, H 5.15. Found: C 66.02, H 5.24.

Acetic acid 5-(2,3,5-trifluorophenyl)-furan-2-ylmethyl ester (14). 1-Bromo-2,3,5-trifluorobenzene (0.211 g, 1 mmol) and acetic acid furan-2-ylmethyl ester (0.280 g, 2 mmol) afford **14** in 60% (0.162 g) yield as an amorphous yellow solid: mp 41−44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 1H), 6.90 (d, J = 3.1 Hz, 1H), 6.88−6.77 (m, 1H), 6.55 (d, J = 3.1 Hz, 1H), 5.11 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 157.7 (dd, J = 244.8, 11.1 Hz), 150.7 (dt, J = 250.9, 13.6 Hz), 150.0, 146.7 (m), 120.9 (m), 113.1, 112.7 (d, J = 12.3 Hz), 107.1 (d, J = 27.7 Hz), 103.8 (dd, J = 27.8, 21.3 Hz), 57.8, 20.8. Elemental analysis calcd (%) for $C_{13}H_9F_3O_3$ (270.20): C 57.79, H 3.36. Found: C 57.70, H 3.40.

2-Methyl-2-[5-(2,4,6-trifluorophenyl)-thiophen-2-yl]-[1,3]-dioxolane (15). 2-Bromo-1,3,5-trifluorobenzene (0.211 g, 1 mmol) and 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (0.340 g, 2 mmol) afford **15** in 69% (0.207 g) yield as an amorphous yellow solid: mp 56−58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 3.8 Hz, 1H), 7.05 (d, J = 3.8 Hz, 1H), 6.76 (t, J = 8.5 Hz, 2H), 4.12−3.97 (m, 4H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (dt, J = 250.3, 16.0 Hz), 159.8 (ddd, J = 252.0, 14.5, 9.8 Hz), 148.8 (t, J = 3.1 Hz), 128.9 (t, J = 5.2 Hz), 127.9, 124.0, 108.9 (m), 107.2, 100.7 (tm, J = 28.5 Hz), 65.0, 27.6. Elemental analysis calcd (%) for $C_{14}H_{11}F_3O_2S$ (300.30): C 55.99, H 3.69. Found: C 56.14, H 3.79.

2-[5-(3,5-Difluorophenyl)-thiophen-2-yl]-2-methyl-[1,3]-dioxolane (16). 1-Bromo-3,5-difluorobenzene (0.193 g, 1 mmol) and 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (0.340 g, 2 mmol) afford **16** in 69% (0.194 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 3.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 3.8 Hz, 1H), 6.70 (tt, J = 7.8, 2.1 Hz, 1H), 4.12−3.97 (m, 4H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (dd, J = 248.2, 3.1 Hz), 148.4, 141.2 (t, J = 2.9 Hz), 137.4 (t, J = 10.5 Hz), 125.1, 124.2, 108.4 (d, J = 18.9 Hz), 107.0, 102.5 (t, J = 25.5 Hz), 65.0, 27.4. Elemental analysis calcd (%) for $C_{14}H_{12}F_2O_2S$ (282.31): C 59.56, H 4.28. Found: C 59.41, H 4.14.

5-(3,5-Difluorophenyl)-2-ethyl-4-methyl-thiazole (17). 1-Bromo-3,5-difluorobenzene (0.193 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) afford **17** in 80% (0.191 g) yield as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 8.4 Hz, 2H), 6.75 (tt, J = 7.8, 2.1 Hz, 1H), 3.00 (q, J = 7.3 Hz, 2H), 2.47 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 162.9 (dd, J = 249.0, 13.2 Hz), 148.2, 135.5 (t, J = 10.3 Hz), 128.5 (t, J = 2.8 Hz), 111.9 (d, J = 18.8 Hz), 102.8 (t, J = 25.3 Hz), 26.9, 16.2, 14.2. Elemental analysis calcd (%) for $C_{12}H_{11}F_2NS$ (239.29): C 60.23, H 4.63. Found: C 60.14, H 4.72.

General Procedure for Palladium-Catalyzed Direct Arylations of 1a, 4, 6, 10, and 17. The reaction of the aryl bromide (1.5 mmol), **1a**, **4**, **6**, **10**, or **17** (1 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 20 h in DMAc (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$[14] (12.2 mg, 0.02 mmol) under argon affords the coupling products **18**−**29** after evaporation of the solvent and purification on silica gel. Eluent pentane:diethylether 9:1 for compounds **18**, **24**; pentane:diethylether 4:1 for compounds **25**, **27**−**29**; pentane:diethylether 3:2 for compounds **19**, **20**, **22**, **26**; pentane:diethylether 7:3 for compounds **21**, **23**.

2′,3′,5′,6′-Tetrafluoro-4′-[5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-biphenyl-4-carbaldehyde (18). 2-Methyl-2-[5-(2,3,5,6-tetrafluorophenyl)-thiophen-2-yl]-[1,3]dioxolane **1a** (0.318 g, 1 mmol) and 4-bromobenzaldehyde (0.278 g, 1.5 mmol) afford **18** in 76% (0.321 g) yield as an amorphous white solid: mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 3.8 Hz, 1H), 7.13 (d, J = 3.8 Hz, 1H), 4.14−3.97 (m, 4H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 150.9 (m), 144.0 (dm, J = 250.0 Hz, 4C), 136.4, 133.4, 130.9, 130.6 (t, J = 6.3 Hz), 129.7, 127.1 (m), 124.4, 117.2 (m), 114.3 (m), 65.1, 27.6. Elemental analysis calcd (%) for $C_{21}H_{14}F_4O_3S$ (422.39): C 59.71, H 3.34. Found: C 59.81, H 3.24.

1-{2′,3′,5′,6′-Tetrafluoro-4′-[5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-biphenyl-3-yl}-ethanone (19). 2-Methyl-2-[5-(2,3,5,6-tetrafluorophenyl)-thiophen-2-yl]-[1,3]dioxolane **1a** (0.318 g, 1 mmol) and 3-bromoacetophenone (0.298 g, 1.5 mmol) afford **19** in 75% (0.327 g) yield as an amorphous yellow solid: mp 84−86 °C; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 3.8 Hz, 1H), 7.12 (d, J = 3.8 Hz, 1H), 4.14−3.97 (m, 4H), 2.65 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 150.7, 144.0 (dm, J = 250.0 Hz, 4C), 137.5, 134.6, 130.5 (t, J = 4.0 Hz), 130.1, 129.0, 128.9, 127.9, 127.2 (m), 124.4, 107.1, 65.1, 27.6, 26.6. Elemental analysis calcd (%) for $C_{22}H_{16}F_4O_3S$ (436.42): C 60.55, H 3.70. Found: C 60.41, H 3.89.

3-{2,3,5,6-Tetrafluoro-4-[5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-phenyl}-pyridine (20). 2-Methyl-2-[5-(2,3,5,6-tetrafluorophenyl)-thiophen-2-yl]-[1,3]dioxolane **1a** (0.318 g, 1 mmol) and 3-bromopyridine (0.237 g, 1.5 mmol) afford **20** in 66% (0.261 g) yield as an amorphous yellow solid: mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.70 (d, J = 3.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 3.8 Hz, 1H), 7.45 (dd, J = 7.8, 5.0 Hz, 1H), 7.12 (d, J = 3.8 Hz, 1H), 4.12−3.98 (m, 4H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9 (t, J = 3.9 Hz), 150.5, 150.1, 145.3 (dm, J = 250.0 Hz, 4C), 137.4, 130.6 (t, J = 6.1 Hz), 127.0 (m), 124.4, 123.9, 123.5, 115.1 (t, J = 16.8 Hz), 114.4 (t, J = 14.8 Hz), 107.1, 65.1, 27.6. Elemental analysis calcd (%) for $C_{19}H_{13}F_4NO_2S$ (395.37): C 57.72, H 3.31. Found: C 57.50, H 3.58.

Ethyl 4′-(2-ethyl-4-methylthiazol-5-yl)-2′,3′,5′,6′-tetrafluoro-biphenyl-4-carboxylate (21). 2-Ethyl-4-methyl-5-(2,3,5,6-tetrafluorophenyl)-thiazole **5** (0.275 g, 1 mmol) and ethyl 4-bromobenzoate (0.343 g, 1.5 mmol) afford **21** in 80% (0.338 g) yield as an amorphous yellow solid: mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 4.42 (q, J = 7.3 Hz, 2H), 3.06 (q, J = 7.3 Hz, 2H), 2.37 (s, 3H), 1.48−1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 165.9, 152.8, 144.2 (dm, J = 250.0 Hz, 4C), 131.6, 131.3, 130.2, 129.8, 119.8 (t, J = 16.4 Hz), 113.8, 111.8 (t, J = 18.3 Hz), 61.3, 27.0, 16.2, 14.3, 14.0. Elemental analysis calcd (%) for $C_{21}H_{17}F_4NO_2S$ (423.42): C 59.57, H 4.05. Found: C 59.60, H 3.89.

4′-(2-Ethyl-4-methylthiazol-5-yl)-2′,3′,5′,6′-tetrafluorobiphenyl-3-carbonitrile (22). 2-Ethyl-4-methyl-5-(2,3,5,6-tetrafluorophenyl)-thiazole **5** (0.275 g, 1 mmol) and 3-bromobenzonitrile (0.273 g, 1.5 mmol) afford **22** in 72% (0.271 g) yield as an amorphous yellow solid: mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.50 (m, 4H), 3.00 (q, J = 7.3 Hz, 2H), 2.30 (s, 3H), 1.37 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 152.9, 144.0 (dm, J = 250.0 Hz, 4C), 134.4, 133.6, 132.8, 129.7, 128.6, 118.3 (t, J = 16.2 Hz), 118.0, 113.6, 112.7, 112.5 (t, J = 17.4 Hz), 27.0, 16.2, 14.0. Elemental analysis calcd (%) for $C_{19}H_{12}F_4N_2S$ (376.37): C 60.63, H 3.21. Found: C 60.47, H 3.02.

2-*n*-Butyl-5-(2,3,5,6-tetrafluoro-4-naphthalen-2-ylphenyl)-furan (23). 2-*n*-Butyl-5-(2,3,5,6-tetrafluorophenyl)-furan **6** (0.272 g, 1 mmol) and 2-bromonaphthalene (311 g, 1.5 mmol) afford **23** in 66% (0.263 g) yield as an amorphous yellow solid: mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.85 (m, 4H), 7.60−7.53 (m, 3H), 6.90 (d, J = 3.1 Hz, 1H), 6.21 (d, J = 3.1 Hz, 1H), 2.75 (t, J = 7.3 Hz, 2H), 1.71 (quint., J = 7.3 Hz, 2H), 1.45 (sext., J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 144.9 (dm, J = 250.0 Hz, 2C), 142.5 (dm, J = 250.0 Hz, 2C), 140.6 (m), 133.2, 133.0, 130.0, 128.3, 128.2, 127.7, 127.2, 127.0, 126.5, 124.9, 117.9 (t, J = 16.8 Hz), 114.9 (t, J = 6.7 Hz), 110.4 (t, J = 13.8 Hz), 107.1, 30.0, 27.8, 22.2, 13.8. Elemental analysis calcd (%) for $C_{24}H_{18}F_4O$ (398.39): C 72.35, H 4.55. Found: C 72.54, H 4.36.

2-*n*-Butyl-5-(2,3,5,6-tetrafluoro-3′-nitrobiphenyl-4-yl)-furan (24). 2-*n*-Butyl-5-(2,3,5,6-tetrafluorophenyl)-furan **6** (0.272 g, 1 mmol) and 1-bromo-3-nitrobenzene (0.303 g, 1.5 mmol) afford **24** in 71% (0.279 g) yield as an amorphous yellow solid: mp 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 3.1 Hz, 1H), 6.21 (d, J = 3.1 Hz, 1H), 2.75 (t, J = 7.3 Hz, 2H), 1.71 (quint., J = 7.3 Hz, 2H), 1.45 (sext., J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 148.4, 142.5 (dm, J = 250.0 Hz), 144.8 (d, J = 250.0 Hz), 140.2 (m), 136.1, 129.7, 129.2, 125.3, 123.9, 115.7 (t, J = 6.8 Hz), 115.1 (t, J = 16.8 Hz), 111.7 (t, J = 12.0 Hz), 107.3, 29.9, 27.8, 22.2, 13.8. Elemental analysis calcd (%) for $C_{20}H_{15}F_4NO_3$ (393.33): C 61.07, H 3.84. Found: C 61.18, H 3.97.

2′,3′,6′-Trifluoro-4′-[5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-biphenyl-4-carbaldehyde (25). 2-Methyl-2-[5-(2,3,5-trifluorophenyl)-thiophen-2-yl]-[1,3]dioxolane **10** (0.300 g, 1 mmol) and 4-bromobenzaldehyde (0.278 g, 1.5 mmol) afford **25** in 81% (0.327 g) yield as an amorphous yellow solid: mp 103−105 °C.^{1}H NMR (400 MHz, Acetone-d_6) δ 10.15 (s, 1H), 8.09 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 3.8 Hz, 1H), 7.58−7.50 (m, 1H), 7.16 (d, J = 3.8 Hz, 1H), 4.12−3.97 (m, 4H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 193.5, 156.8 (dm, J = 244.8 Hz), 152.6 (d, J = 4.7 Hz), 150.3 (dm, J = 250.9 Hz), 146.0 (dm, J = 248.0 Hz), 138.7, 135.8, 135.4 (m), 132.9, 131.3, 129.9 (d, J = 5.3 Hz), 126.9, 125.9 (t, J = 10.2 Hz), 119.1 (m), 111.2 (d, J = 27.0 Hz), 108.6, 66.8, 28.7. Elemental analysis calcd (%) for $C_{21}H_{15}F_3O_3S$ (404.40): C 62.37, H 3.74. Found: C 62.18, H 3.60.

3-{2,3,6-Trifluoro-4-[5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-phenyl}-pyridine (26). 2-Methyl-2-[5-(2,3,5-trifluorophenyl)-thiophen-2-yl]-[1,3]dioxolane **10** (0.300 g, 1 mmol) and 3-bromopyridine (0.237 g, 1.5 mmol) afford **26** in 55% (0.207 g) yield as an amorphous yellow solid: mp 99−101 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.77 (s, 1H), 8.68 (d, J = 3.7 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 3.8 Hz, 1H), 7.59−7.50 (m, 2H), 7.16 (d, J = 3.8 Hz, 1H), 4.12−3.97 (m, 4H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 152.6 (d, J = 4.7 Hz), 152.3 (m), 151.8, 147.0 (dm, J = 250.9 Hz), 139.3, 137.2 (dm, J = 250.9 Hz), 135.3, 129.9 (d, J = 5.3 Hz), 126.9, 126.3, 125.9 (t, J = 11.9 Hz), 117.0 (m), 111.1 (d, J = 27.0 Hz), 108.5, 66.8, 28.7. Elemental analysis calcd (%) for $C_{19}H_{14}F_3NO_2S$ (377.38): C 60.47, H 3.74. Found: C 60.40, H 3.91.

5-(2,6-Difluoro-4′-nitrobiphenyl-4-yl)-2-ethyl-4-methylthiazole (27). 5-(3,5-Difluorophenyl)-2-ethyl-4-methylthiazole **17** (0.239 g, 1 mmol) and 1-bromo-4-nitrobenzene (0.303 g, 1.5 mmol) afford **27** in 70% (0.252 g) yield as an amorphous yellow solid: mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 3.02 (q, J = 7.3 Hz, 2H), 2.54 (s, 3H), 1.42 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.6 (dd, J = 250.8, 7.8 Hz), 148.7, 147.6, 135.5, 135.4 (t, J = 8.3 Hz), 131.3, 128.1 (t, J = 2.8 Hz), 123.5, 115.0 (t, J = 17.8 Hz), 112.3 (d, J = 19.8 Hz), 26.9, 16.4, 14.2. Elemental analysis calcd (%) for $C_{18}H_{14}F_2N_2O_2S$ (360.38): C 59.99, H 3.92. Found: C 60.11, H 3.78.

5-(4′-Chloro-2,6-difluorobiphenyl-4-yl)-2-ethyl-4-methylthiazole (28). 5-(3,5-Difluorophenyl)-2-ethyl-4-methylthiazole **17** (0.239 g, 1 mmol) and 1-bromo-4-chloro-benzene (0.286 g, 1.5 mmol) afford **28** in 77% (0.269 g) yield as an amorphous yellow solid: mp 67−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.42 (m, 4H), 7.06 (d, J = 8.0 Hz, 2H), 3.01 (q, J = 7.3 Hz, 2H), 2.52 (s, 3H), 1.41 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.6 (dd, J = 250.8, 7.8 Hz), 148.4, 134.5, 134.4 (t, J = 8.3 Hz), 131.5, 128.6, 128.4, 127.1, 115.0 (m), 112.2 (d, J = 19.8 Hz), 26.9, 16.4, 14.2. Elemental analysis calcd (%) for $C_{18}H_{14}ClF_2NS$ (349.83): C 61.80, H 4.03. Found: C 61.89, H 3.94.

4′-(2-Ethyl-4-methylthiazol-5-yl)-2′,6′-difluorobiphenyl-2-carbonitrile (29). 5-(3,5-Difluorophenyl)-2-ethyl-4-methylthiazole **17** (0.239 g, 1 mmol) and 2-bromobenzonitrile (0.273 g, 1.5 mmol) afford **29** in 76% (0.258 g) yield as an amorphous yellow solid: mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.60−7.50 (m, 2H), 7.11 (d, J = 8.4 Hz, 2H), 3.02 (q, J = 7.3 Hz, 2H), 2.54 (s, 3H), 1.42 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.7 (dd, J = 250.8, 7.8 Hz), 148.7, 135.9 (t, J = 10.9 Hz), 133.1, 132.7, 132.5, 131.7, 129.0, 128.2, 117.5, 114.1, 114.0 (t, J = 18.8 Hz), 112.2 (d, J = 19.8 Hz), 26.9, 16.4, 14.2. Elemental analysis calcd (%) for $C_{19}H_{14}F_2N_2S$ (340.39): C 67.04, H 4.15. Found: C 67.19, H 4.01.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **1**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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