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Pd-catalyzed direct arylation of 3-fluorofurans utilizing the neighboring effect of fluorine atom: facile synthesis of tetrasubstituted monofluoro furans

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ABSTRACT

Pd-catalyzed direct arylation of 3-fluorofurans with a variety of aryl bromides was facilitated by the neighboring effect of fluorine atom to provide tetrasubstituted monofluoro furans in moderate to good yields.

1. Introduction

Transition-metal-catalyzed direct arylation of aromatic compounds via C–H bond activation enables facile synthesis of useful biaryl compounds, and thus has become one of the focuses of organic synthesis in recent years.[1] In this field, heterocyclic arenes have received particular attentions as substitutes for the pre-activated organometallic partners typically used in conventional cross-coupling reactions due to their peculiar electronic and structural properties.[1] However, in contrast to the numerous related studies on nitrogen-[1c,2] or sulfur-containing[3] heterocyclic arenes, there are only rather limited examples dealing with furans and the reactive sites are mostly restricted to the C2 or C5 postion.[4] Very recently, Hammond et al.[5] has realized arylation at the C4-position of 3-fluorofurans via a microwave promoted Suzuki cross-coupling reaction between 4-iodo-3-fluorofurans and aryl boronic acids, which adds to the limited methods available for the synthesis of multi-substituted fluorous furans.[6] On the other hand, Fagnou et al.[7] and Do and Daugulis[8] have recently realized palladium- and copper-catalyzed direct arylation of perfluoroarenes, respectively, which well demonstrated the special role that the fluorine atom could play in this type of reactions. However, examples with fluoro-heterocyclic compounds are rare, especially in the cases of monofluoro compounds. Based on these studies and our own experience[9] with the chemistry of 3-fluorofurans, we reasoned that the direct arylation at the C4-position of these compounds may be possible and would provide a more atom-economical alternative to existing methods. Herein, we report the details of our research with this strategy.

2. Results and discussion

As a test reaction, the coupling of 3-fluoro-2,5-diphenylfuran **1a** with 1-bromo-4-chlorobenzene was initially studied with several different Pd catalysts, bases, and solvents at varied temperatures (Table 1). It was found that $Pd(OAc)_2$, the most frequently used Pd catalyst for this type of reactions,[1] failed to effect the reaction (Table 1, entries 1 and 2). $PdCl_2$ or $Pd(PPh_3)_4$ also proved unsuitable under the examined reaction conditions (Table 1, entries 3 and 6). Incomplete conversion of **1a** was observed with $PdCl_2(PhCN)_2$ or $Pd_3(dba)_2$, which provided the desired product **2e** in 10% and 26% yields, respectively (Table 1, entries 4 and 5). To our delight, when the reaction was performed with 10 mol % of $PdCl_2(PPh_3)_2$ and 2 equiv of KOAc in DMF, the desired product was obtained in 60% yield (Table 1, entry 8). A slight higher yield (62% yield) was obtained when NMP was employed as the solvent (Table 1, entry 9). Contrastingly, when apolar toluene was used as the solvent or K_2CO_3 was used as the base, the reaction hardly proceeded (Table 1, entries 7 and 12). Moreover, either reducing the amount of $PdCl_2(PPh_3)_2$ to 5 mol % or employing NaOAc as the base led to

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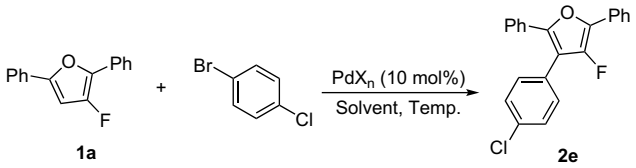
Table 1
Optimization studies for the Pd-catalyzed arylation of **1a**[a]



Entry	Catalytic system	Temp	Solvent	Yield[b]
1	$Pd(OAc)_2$ (10 mol %)+3 equiv NaOAc	80 °C	DMSO	n.r.
2	$Pd(OAc)_2$ (10 mol %)+2 equiv K_2CO_3+50 mol % TBAB[c]+20 mol % PPh_3	80 °C	CH_3CN/H_2O =9:1	Trace
3	$PdCl_2$ (10 mol %)+2 equiv KOAc	110 °C	DMF	n.r.
4	$PdCl_2(PhCN)_2$ (10 mol %)+2 equiv KOAc	110 °C	DMF	10%
5	$Pd_3(dba)_2$ (10 mol %)+2 equiv KOAc	110 °C	DMF	26%
6	$Pd(PPh_3)_4$ (10 mol %)+2 equiv K_2CO_3	110 °C	DMF	Trace
7	$PdCl_2(PPh_3)_2$ (10 mol %)+2 equiv KOAc	110 °C	Toluene	Trace
8	$PdCl_2(PPh_3)_2$ (10 mol %)+2 equiv KOAc	110 °C	DMF	60%
9	$PdCl_2(PPh_3)_2$ (10 mol %)+2 equiv KOAc	110 °C	NMP[c]	62%
10	$PdCl_2(PPh_3)_2$ (5 mol %)+2 equiv KOAc	110 °C	NMP	61%
11	$PdCl_2(PPh_3)_2$ (10 mol %)+2 equiv NaOAc	110 °C	NMP	59%
12	$PdCl_2(PPh_3)_2$ (10 mol %)+2 equiv K_2CO_3	110 °C	NMP	Trace

[a] Compound **1a**/1-bromo-4-chlorobenzene=1:2.
[b] Isolated yields.
[c] TBAB: tetrabutylamine bromide; NMP: *N*-methyl pyrrolidone.

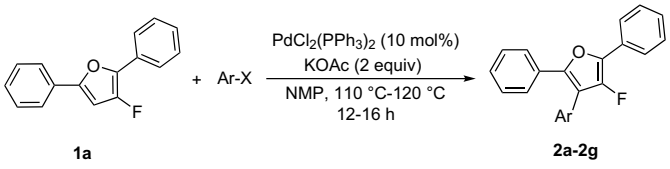
slightly lower yields (Table 1, entries 10 and 11). Thus, the optimum reaction conditions for the present transformation are 10 mol % of $PdCl_2(PPh_3)_2$ and 2 equiv of KOAc in NMP at 110 °C.

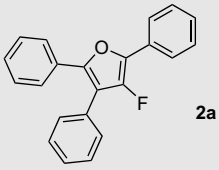
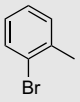
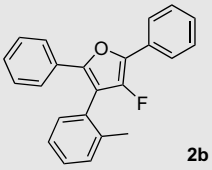
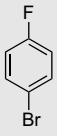
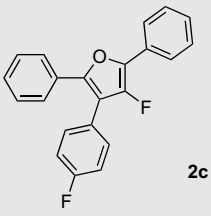
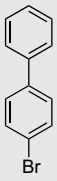
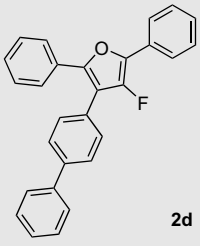
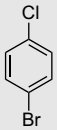
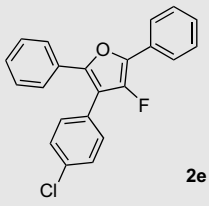
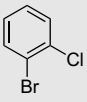
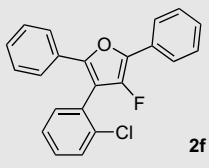
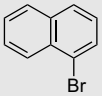
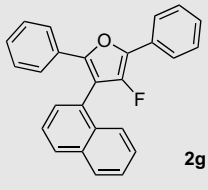
With the optimized conditions in hand, the coupling reactions of 3-fluoro-2,5-diphenylfuran **1a** with a series of aryl halides were then examined (Table 2). In general, most of the examined aryl halides participated in the reaction smoothly and the reaction completed in 12–16 h providing the desired products **2a**–**2g** in 51–73% yields (Table 2, entries 1–8). Neither the electronic nature nor the positions of the substituents on the phenyl ring exerted any considerable influence on the yields. However, in the case of 4-nitrophenyl bromide, a complex mixture was obtained (Table 2, entry 9).

Subsequently, we explored the arylation of different fluoro-substituted furans with 1-bromo-4-chlorobenzene and the results are summarized in Table 3. For substrates **1b**–**1g** bearing substituted groups with different electronic natures on the different positions of R^2, no marked difference in yields (51–65%) was observed (Table 3, entries 1–6). Furthermore, when R^1 or R^2 was an alkyl group, the reaction still proceeded smoothly to provide the desired products without apparent drop in yields (Table 3, entries 7 and 8). Notably, the substrate 2,5-diphenylfuran **1j** without a fluorine atom failed to undergo the reaction, which was in support of the activating role of the neighboring fluorine atom in the present system (Table 3, entry 9). To examine the reaction scope further, substrate 3-fluoro-2,5-diphenylthiophene **1k**, the thiophene counterpart of **1a**, was also prepared and subjected to the same reaction conditions, but no reaction was detected (Table 3, entry 10).

Based on the above experimental results, an electrophilic mechanism similar to those of previous studies on the arylation of heterocycles[11] may be invoked for the present reaction (Scheme 1). The key step may involve the electrophilic attack on **1** to form the Pd(II) intermediate **A**,[2a] which may explain the failure of substrate **1k** to undergo the reaction for that thiophenes in general are more electron-deficient than furans.[12] Subsequent abstraction of the acidic hydrogen atom in **A** with the help of a base would generate another intermediate **B**, which would then undergo reductive elimination to deliver the desired products **2** and release the Pd catalyst. The presence of the fluorine atom in **1** may not only

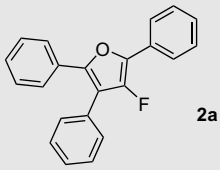
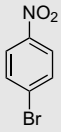
Table 2
Scope study of different aryl bromides with 3-fluoro-2,5-diphenylfuran (**1a**)[a]



Entry	ArX	Product	Yield[b]
1		 **2a**	51 (%)
2		 **2b**	64 (%)
3		 **2c**	73 (%)
4		 **2d**	52 (%)
5		 **2e**	62 (%)
6		 **2f**	70 (%)
7		 **2g**	55 (%)

(*continued*)

Table 2 (*continued*)

Entry	ArX	Product	Yield[b]
8		 **2a**	53 (%)[c]
9		—[d]	—[d]

[a] Compound **1a**/ArX=1:2.
[b] Isolated yields.
[c] The reaction time was 9 h.
[d] The reaction system was complicated.

facilitate the formation of intermediate **A** through conjugative donation of the lone electron pairs, but also could increase the acidity of the hydrogen atom in **A** to form **B** due to its high electronegativity. However, the determination of the exact reaction mechanism as well as the role of the fluorine atom still requires further investigation.

3. Conclusion

In summary, we have successfully utilized the neighboring effect of the fluorine atom for functionalization at the C4 position of 3-fluorofurans to synthesize tetrasubstituted monofluoro furans via direct Pd-catalyzed arylation reactions. Using 10 mol % of $PdCl_2(PPh_3)_2$ as the catalyst, 2 equiv of KOAc as the base, and NMP as the solvent, the desired products were obtained in 51–73% yields within 12–16 h at 110 °C.

4. Experimental

4.1. General

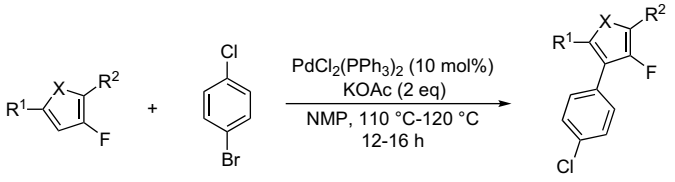
^1H and ^{13}C NMR spectra were recorded at 300 and 100 MHz, respectively, with TMS as the internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as the external standard. IR spectra were recorded in cm^{-1}. Melting points were uncorrected. All solvents were distilled prior to use unless otherwise noted. All reactions sensitive to moisture or oxygen were conducted under an atmosphere of nitrogen or argon.

Compounds **1a**–**1j** were prepared according to the known procedures.[9,10]

4.2. General procedure for the preparation of 2,4,5-trisubstituted 3-fluorofurans 2

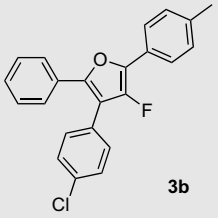
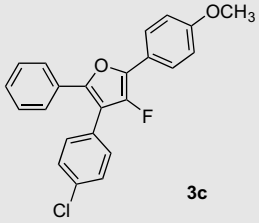
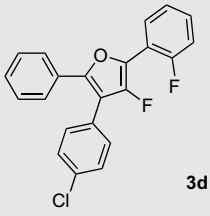
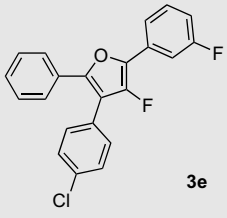
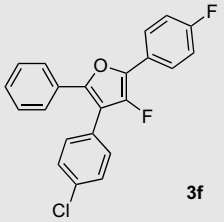
Under an atmosphere of argon, compound **1** (0.2 mmol), aryl bromide (0.4 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and KOAc (39.2 mg, 0.4 mmol) were mixed together. Then 3 mL of *N*-methyl pyrrolidin-2-one (NMP) was added, the system was then heated to 120 °C for appropriate times. When the reaction was completed (monitored by TLC), the reaction system was cooled to room temperature and 3 mL of saturated aqueous NH_4Cl was added to quench the reaction. After extraction with Et_2O and drying with Na_2SO_4, the organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired products.

Table 3
Scope study of different **1** with 1-bromo-4-chlorobenzene[a]



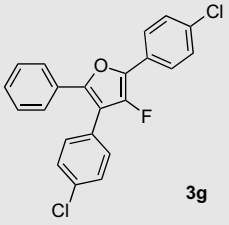
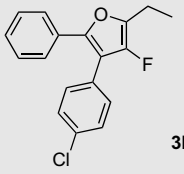
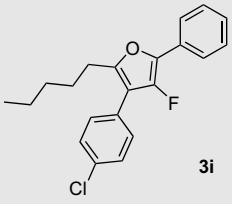
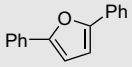
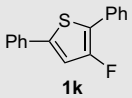
1b-1j X = O
1k X = S

3b-3i

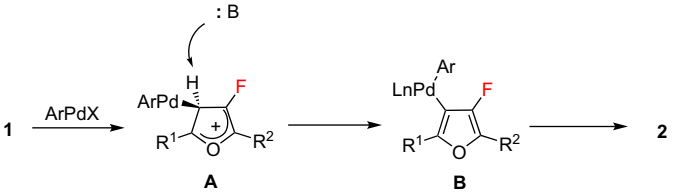
Entry	Reactant		Product	Yield[b]
	R^1	R^2		
1	Ph (**1b**)	*p*-$CH_3C_6H_4$	 **3b**	60 (%)
2	Ph (**1c**)	*p*-$CH_3OC_6H_4$	 **3c**	51 (%)
3	Ph (**1d**)	*o*-FC_6H_4	 **3d**	57 (%)
4	Ph (**1e**)	*m*-FC_6H_4	 **3e**	60 (%)
5	Ph (**1f**)	*p*-FC_6H_4	 **3f**	59 (%)

(*continued on next page*)

Table 3 (*continued*)

Entry	Reactant		Product	Yield[b]
	R^1	R^2		
6	Ph (**1g**)	*p*-ClC_6H_4	 **3g**	65 (%)
7	Ph (**1h**)	Et	 **3h**	57 (%)
8	*n*-Pentyl(**1i**)	Ph	 **3i**	61 (%)
9	 **1j**		—[c]	—[c]
10	 **1k**		—[c]	—[c]

[a] Compound **1**/1-bromo-4-chlorobenzene=1:2.
[b] Isolated yields.
[c] No reaction was detected.



Scheme 1. A plausible mechanism for the reaction of **1** with aryl halides.

*4.2.1. 3-Fluoro-2,4,5-triphenylfuran (**2a**)*

Yield: 51%; white solid; the ^1H NMR spectra agree well with that reported.[6b]

*4.2.2. 3-Fluoro-2,5-diphenyl-4-o-tolylfuran (**2b**)*

Yield: 64%; colorless oil; IR (CH_2Cl_2, film): 1640, 1495, 1167, 1126, 1068, 944, 850, 763, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.82 (d, ^3J=8.1 Hz, 2H), 7.48–7.24 (m, 12H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.4 (d, $^1J_{CF}$=253.8 Hz), 146.2 (d, $^3J_{CF}$=5.3 Hz), 137.9, 135.4 (d, $^2J_{CF}$=19.3 Hz), 131.0, 130.7, 129.5, 129.0, 128.9, 128.8, 128.0, 127.4, 126.5, 124.9, 123.8 (d, $^3J_{CF}$=5.2 Hz), 115.4 (d, $^2J_{CF}$=17.9 Hz), 20.2; ^{19}F NMR ($CDCl_3$): δ=−163.0 (s, 1F); MS (EI) (*m*/*z*): 328 (M^+); HRMS calcd for $C_{23}H_{17}FO$: 328.1263, found: 328.1266.

*4.2.3. 3-Fluoro-4-(4-fluorophenyl)-2,5-diphenylfuran (**2c**)*

Yield: 73%; white solid; mp: 127–128 °C; IR (CH_2Cl_2, film): 3056, 1641, 1512, 1494, 1225, 1159, 944, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.80 (d, ^3J=7.5 Hz, 2H), 7.56–7.11 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.5 (d, $^1J_{CF}$=246.4 Hz), 148.6 (d, $^1J_{CF}$=254.6 Hz), 146.8 (d, $^3J_{CF}$=5.3 Hz), 135.5 (d, $^2J_{CF}$=19.4 Hz), 131.4, 131.3, 130.4, 128.8, 128.5, 128.2, 127.2, 125.8, 123.6 (d, $^3J_{CF}$=5.2 Hz), 116.0 (d, $^2J_{CF}$=20.8 Hz), 114.6 (d, $^2J_{CF}$=16.7 Hz); ^{19}F NMR ($CDCl_3$): δ=−113.9 (dd, 1F), −165.1 (s, 1F); MS (EI) (*m*/*z*): 332 (M^+). Anal. Calcd for $C_{22}H_{14}F_2O$ (%): C, 79.51; H, 4.25. Found: C, 79.39; H, 4.39.

*4.2.4. 3-(Biphenyl-4-yl)-4-fluoro-2,5-diphenylfuran (**2d**)*

Yield: 52%; white solid; mp: 174–175 °C; IR (CH_2Cl_2, film): 1680, 1598, 1448, 1278, 989, 846, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.82 (d, ^3J=7.8 Hz, 2H), 7.69–7.26 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.7 (d, $^1J_{CF}$=254.6 Hz), 145.7 (d, $^3J_{CF}$=6.0 Hz), 140.7, 140.5, 135.5 (d, $^2J_{CF}$=19.4 Hz), 130.6, 130.5, 129.9, 128.8, 128.7, 128.5, 128.1, 127.5, 127.4, 127.2, 127.0, 125.9, 124.8, 123.6 (d, $^3J_{CF}$=5.2 Hz), 115.2 (d, $^2J_{CF}$=16.4 Hz); ^{19}F NMR ($CDCl_3$): δ=−164.7 (s, 1F); MS (EI) (*m*/*z*): 390 (M^+); HRMS calcd for $C_{28}H_{19}FO$: 390.1420, found: 390.1424.

*4.2.5. 3-(4-Chlorophenyl)-4-fluoro-2,5-diphenylfuran (**2e**)*

Yield: 62%; pale yellow solid; mp: 109–110 °C; IR (CH_2Cl_2, film): 1643, 1493, 1392, 1194, 1093, 944, 836, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.79 (d, ^3J=7.8 Hz, 2H), 7.57–7.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.3 (d, $^1J_{CF}$=254.6 Hz), 145.8 (d, $^3J_{CF}$=5.9 Hz), 135.7 (d, $^2J_{CF}$=19.4 Hz), 134.0, 130.87, 130.85, 130.3, 129.1, 128.8, 128.7, 128.6, 128.3, 127.3, 125.9, 123.6 (d, $^3J_{CF}$=6.1 Hz), 114.4 (d, $^2J_{CF}$=15.6 Hz); ^{19}F NMR ($CDCl_3$): δ=−165.0 (s, 1F); MS (EI) (*m*/*z*): 348 (M^+); HRMS calcd for $C_{22}H_{14}ClFO$: 348.0717, found: 348.0720.

*4.2.6. 3-(4-Chlorophenyl)-4-fluoro-2,5-diphenylfuran (**2f**)*

Yield: 70%; colorless oil; IR (CH_2Cl_2, film): 3059, 1642, 1598, 1494, 1153, 1219, 944, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.83 (d, ^3J=7.2 Hz, 2H), 7.58–7.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.1 (d, $^1J_{CF}$=255.3 Hz), 146.3 (d, $^3J_{CF}$=6.0 Hz), 135.6 (d, $^2J_{CF}$=18.6 Hz), 135.1, 132.6, 130.6, 130.3, 130.2, 129.4, 129.0, 128.8, 128.3, 127.5, 127.4, 125.2, 123.9, 123.8, 113.5 (d, $^2J_{CF}$=17.9 Hz); ^{19}F NMR ($CDCl_3$): δ=−162.4 (s, 1F); MS (EI) (*m*/*z*): 348 (M^+); HRMS calcd for $C_{22}H_{14}ClFO$: 348.0717, found: 348.0715.

*4.2.7. 3-Fluoro-4-(naphthalen-1-yl)-2,5-diphenylfuran (**2g**)*

Yield: 55%; yellow oil; IR (CH_2Cl_2, film): 3057, 1807, 1597, 1495, 1264, 1155, 932, 765, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.87–7.85 (m, 5H), 7.56–7.45 (m, 9H), 7.18–7.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.5 (d, $^1J_{CF}$=254.6 Hz), 146.2 (d, $^3J_{CF}$=6.0 Hz), 135.2 (d, $^2J_{CF}$=19.3 Hz), 133.8, 132.0, 129.0, 128.7, 128.6, 128.3, 127.7, 127.5 (d, $^4J_{CF}$=1.6 Hz), 127.1 (d, $^4J_{CF}$=1.4 Hz), 126.6, 126.2, 125.6, 125.5, 124.9, 123.5 (d, $^3J_{CF}$=5.2 Hz), 113.8 (d, $^2J_{CF}$=17.9 Hz); ^{19}F NMR ($CDCl_3$): δ=−162.7 (s, 1F); MS (EI) (*m*/*z*): 364 (M^+); HRMS calcd for $C_{26}H_{17}FO$: 364.1263, found: 364.1262.

*4.2.8. 3-(4-Chlorophenyl)-4-fluoro-2-phenyl-5-p-tolylfuran (**3b**)*

Yield: 60%; white solid; mp: 136–137 °C; IR (CH_2Cl_2, film): 1641, 1600, 1509, 1088, 943, 842, 817, 763, 694, 648, 525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.70–7.25 (m, 13H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.0 (d, $^1J_{CF}$=253.1 Hz), 145.3 (d, $^3J_{CF}$=5.2 Hz), 137.2, 136.0 (d, $^2J_{CF}$=19.4 Hz), 133.9, 130.8, 130.4, 129.5, 129.1, 128.7, 128.6, 128.2, 125.9, 123.62, 123.58, 114.4 (d, $^2J_{CF}$=15.6 Hz), 21.4; ^{19}F NMR ($CDCl_3$): δ=−166.1 (s, 1F); MS (EI) (*m*/*z*): 362 (M^+); HRMS calcd for $C_{23}H_{16}ClFO$: 362.0874, found: 362.0877.

*4.2.9. 3-(4-Chlorophenyl)-4-fluoro-5-(4-methoxyphenyl)-2-phenylfuran (**3c**)*

Yield: 52%; light yellow solid; mp: 109–110 °C; IR (CH_2Cl_2, film): 1599, 1508, 1249, 1177, 1073, 942, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.74–7.29 (m, 11H), 7.10–6.98 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.9, 147.3 (d, $^1J_{CF}$=252.3 Hz), 144.9 (d, $^3J_{CF}$=6.0 Hz), 135.8 (d, $^2J_{CF}$=19.1 Hz), 133.9, 130.8, 130.4 (d, $^4J_{CF}$=2.3 Hz), 129.4, 128.5, 128.4 (d, $^4J_{CF}$=3.0 Hz), 128.0, 125.6, 125.13, 125.08, 121.6 (d, $^3J_{CF}$=5.2 Hz), 114.3 (d, $^2J_{CF}$=15.6 Hz), 55.3; ^{19}F NMR ($CDCl_3$): δ=−167.7 (s, 1F); MS (EI) (*m*/*z*): 378 (M^+). Anal. Calcd for $C_{23}H_{16}ClFO_2$ (%): C, 72.92; H, 4.26. Found: C, 73.01; H, 4.11.

*4.2.10. 3-(4-Chlorophenyl)-4-fluoro-5-(2-fluorophenyl)-2-phenylfuran (**3d**)*

Yield: 57%; light yellow solid; mp: 106–107 °C; IR (CH_2Cl_2, film): 1639, 1494, 1449, 1233, 842, 766, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.75–7.13 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.2 (d, $^1J_{CF}$=251.9 Hz), 148.6 (d, $^1J_{CF}$=256.9 Hz), 147.1 (d, $^3J_{CF}$=5.1 Hz), 134.1, 131.4 (d, $^2J_{CF}$=20.5 Hz), 130.9, 130.1, 129.4 (d, $^3J_{CF}$=8.1 Hz), 129.1, 128.6, 128.5, 128.2 (d, $^4J_{CF}$=2.2 Hz), 127.3 (m, *J*=3.0 Hz), 126.0, 124.3 (d, $^4J_{CF}$=3.6 Hz), 116.8 (dd, $^2J_{CF}$=14.2 Hz, $^3J_{CF}$=5.1 Hz), 116.4 (d, $^2J_{CF}$=21.2 Hz), 114.2 (d, $^2J_{CF}$=16.0 Hz); ^{19}F NMR ($CDCl_3$): δ=−113.0 (m, 1F), −161.0 (d, J_{FF}=244.5 Hz, 1F); MS (EI) (*m*/*z*): 366 (M^+); HRMS calcd for $C_{22}H_{13}ClF_2O$: 366.0623, found: 366.0627.

*4.2.11. 3-(4-Chlorophenyl)-4-fluoro-5-(3-fluorophenyl)-2-phenylfuran (**3e**)*

Yield: 60%; light yellow solid; mp: 86–87 °C; IR (CH_2Cl_2, film): 1638, 1500, 1430, 1269, 1198, 882, 778, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.56–6.95 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.1 (d, $^1J_{CF}$=244.6 Hz), 149.0 (d, $^1J_{CF}$=256.2 Hz), 146.4 (d, $^3J_{CF}$=5.8 Hz), 134.6 (d, $^2J_{CF}$=21.9 Hz), 130.8, 130.5, 130.4, 130.0, 129.2, 128.64, 128.57, 127.9 (d, $^4J_{CF}$=2.2 Hz), 126.0, 119.2 (m), 114.4 (d, $^2J_{CF}$=16.1 Hz) 114.1 (d, $^2J_{CF}$=21.1 Hz), 110.4 (dd, $^2J_{CF}$=24.1 Hz, $^3J_{CF}$=5.1 Hz); ^{19}F NMR ($CDCl_3$): δ=−113.0 (dd, J_{FF}=15.8, 9.9 Hz, 1F), −163.2 (s, 1F); MS (EI) (*m*/*z*): 366 (M^+); HRMS calcd for $C_{22}H_{13}ClF_2O$: 366.0623, found: 366.0626.

*4.2.12. 3-(4-Chlorophenyl)-4-fluoro-5-(4-fluorophenyl)-2-phenylfuran (**3f**)*

Yield: 59%; white solid; mp: 113–114 °C; IR (CH_2Cl_2, film): 1508, 1235, 1093, 943, 831, 816, 761, 689, 653, 510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.77–7.53 (m, 2H), 7.52–7.15 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.8 (d, $^1J_{CF}$=246.4 Hz), 148.0 (d, $^1J_{CF}$=255.3 Hz), 145.7 (d, $^3J_{CF}$=5.2 Hz), 134.9 (d, $^2J_{CF}$=19.3 Hz), 134.0, 130.7, 130.1, 129.0, 128.5, 128.3, 128.0, 125.8, 125.4 (d, $^3J_{CF}$=5.2 Hz), 125.3 (d, $^3J_{CF}$=5.3 Hz), 115.8 (d, $^2J_{CF}$=21.6 Hz), 114.3 (d, $^2J_{CF}$=16.4 Hz); ^{19}F NMR ($CDCl_3$): δ=−113.9 (s, 1F), −165.9 (s, 1F); MS (EI) (*m*/*z*): 366 (M^+); HRMS calcd for $C_{22}H_{13}ClF_2O$: 366.0623, found: 366.0624.

*4.2.13. 2,4-Bis(4-chlorophenyl)-3-fluoro-5-phenylfuran (**3g**)*

Yield: 65%; light yellow solid; mp: 140–142 °C; IR (CH_2Cl_2, film): 1639, 1501, 1392, 1090, 942, 826, 702, 691, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.70 (d, ^3J=7.5 Hz, 2H), 7.55–7.26 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.6 (d, $^1J_{CF}$=256.1 Hz), 146.1 (d, $^3J_{CF}$=6.0 Hz), 134.8 (d, $^2J_{CF}$=19.3 Hz), 134.1, 132.9, 130.8, 130.0 (d, $^4J_{CF}$=2.4 Hz), 129.1, 129.0, 128.6, 128.5, 127.9 (d, $^4J_{CF}$=2.2 Hz), 127.1 (d, $^4J_{CF}$=4.5 Hz), 126.0, 124.7 (d, $^3J_{CF}$=5.2 Hz), 114.4 (d, $^2J_{CF}$=15.7 Hz); ^{19}F NMR ($CDCl_3$): δ=−164.1 (s, 1F); MS (EI) (*m*/*z*): 382 (M^+); HRMS calcd for $C_{22}H_{13}Cl_2FO$: 382.0327, found: 382.0328.

*4.2.14. 3-(4-Chlorophenyl)-5-ethyl-4-fluoro-2-phenylfuran (**3h**)*

Yield: 57%; yellow oil; IR (CH_2Cl_2, film): 2976, 3939, 1704, 1676, 1588, 1448, 1092, 1016, 813, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.46–7.24 (m, 9H), 2.75 (q, ^3J=7.8 Hz, 2H), 1.31 (t, ^3J=7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.3 (d, $^1J_{CF}$=246.4 Hz), 144.7 (d, $^3J_{CF}$=6.0 Hz), 138.9 (d, $^2J_{CF}$=14.6 Hz), 133.5, 130.7, 129.0, 128.9, 128.5, 128.2, 127.8, 125.7, 113.1 (d, $^2J_{CF}$=16.4 Hz), 18.4 (d, $^3J_{CF}$=3.7 Hz), 11.9; ^{19}F NMR ($CDCl_3$): δ=−174.3 (s, 1F); MS (EI) (*m*/*z*): 300 (M^+); HRMS calcd for $C_{18}H_{14}ClFO$: 300.0717, found: 300.0716.

*4.2.15. 3-(4-Chlorophenyl)-4-fluoro-2-pentyl-5-phenylfuran (**3i**)*

Yield: 61%; yellow oil; IR (CH_2Cl_2, film): 2959, 1558, 1495, 1454, 1091, 1004, 959, 761, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.71–7.24 (m, 9H), 2.72 (t, *J*=7.8 Hz, 2H), 1.74–1.69 (m, 2H), 1.34–1.31 (m, 4H), 0.89 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.4 (d, $^3J_{CF}$=5.2 Hz), 147.8 (d, $^1J_{CF}$=254.6 Hz), 134.8 (d, $^2J_{CF}$=20.1 Hz), 133.4, 130.1, 129.3, 129.1, 128.9, 128.4, 127.0, 123.5 (d, $^3J_{CF}$=4.4 Hz), 114.0 (d, $^2J_{CF}$=14.9 Hz), 31.6, 28.7, 27.5, 22.6 14.2; ^{19}F NMR ($CDCl_3$): δ=−166.5 (s, 1F); MS (EI) (*m*/*z*): 342 (M^+); HRMS calcd for $C_{21}H_{20}ClFO$: 342.1187, found: 342.1190.

*4.2.16. Preparation of 3-fluoro-2,5-diphenylthiophene (**1k**)*

To a solution of 2,2-difluoro-1,4-diphenylbut-3-yn-1-ol (**4**)[6b] (258 mg, 1 mmol) in 5 mL of CH_2Cl_2 in an ice bath was added 0.33 mL of Et_3N (2.3 mmol), and the solution was stirred for about 10 min before methanesulfonyl chloride (0.12 mL, 1.5 mmol) was added slowly. Then the mixture was stirred at this temperature for 3 h (monitored by TLC). Saturated NH_4Cl (2 mL) was added to quench the reaction and the reaction mixture was extracted with CH_2Cl_2. After removal of the solvent in vacuum, the residue was dissolved in 3 mL of acetone and NaSH (90 mg, 1.6 mmol) was added at room temperature. After stirring for one day, 5 mL of NH_4Cl was added to quench the reaction. After removal of the volatile substance, the remaining aqueous layer was extracted with ether acetate, dried over Na_2SO_4, concentrated in vacuum, and purified by column chromatography on silica gel to afford 3-fluoro-2,5-diphenylthiophenerd (**1k**) in 28% yield.

Yield: 28%; white solid; mp: 95–96 °C; IR (CH_2Cl_2, film): 1573, 1561, 1395, 1011, 819, 719, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.68–7.58 (m, 4H), 7.44–7.26 (m, 6H), 7.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.9 (d, $^1J_{CF}$=260.5 Hz), 139.8 (d, $^2J_{CF}$=9.0 Hz), 133.6, 131.4, 129.1, 129.0, 128.3, 127.5, 126.7 (d, $^3J_{CF}$=5.8 Hz), 125.2, 120.8 (d, $^3J_{CF}$=11.9 Hz), 114.6 (d, $^2J_{CF}$=27.5 Hz); ^{19}F NMR ($CDCl_3$): δ=−126.9 (s, 1F); MS (EI) (*m*/*z*): 254 (M^+); HRMS calcd for $C_{16}H_{11}FS$: 254.0566, found: 254.0567.

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