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N-Heterocyclic Carbene-Palladium(II)-1-Methylimidazole Complex Catalyzed Direct C-H Bond Arylation of Benzo[*b*]furans with Aryl Chlorides

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ABSTRACT: The first example of sole direct C-H bond arylation of benzo[*b*]furans with aryl chlorides was achieved catalyzed by a well-defined NHC-Pd(II)-Im complex. Under the suitable conditions, all reactions involving kinds of benzo[*b*]furans and (hetero)aryl chlorides proceeded well to give the desired C2-arylated benzo[*b*]furans in sole regioselectivity in acceptable to high yields, providing an efficient and economic pathway for the direct C2-H bond arylation of benzo[*b*]furans.

KEYWORDS: *N*-heterocyclic carbene-palladium complex; C-H bond arylation; benzo[*b*]furans; aryl chlorides; synthetic method

2-Aryl benzo[*b*]furans are very important backbones in organic chemistry and many of their derivatives possess medicinal and biological activities.[1] Consequently, to develop efficient strategy for the synthesis of 2-aryl benzo[*b*]furans is of great importance. Classical method for the synthesis of such compounds is the cyclization strategy (including the coupling-cyclization processes).[2] In addition, as a complement, some examples on the transition metal catalyzed cross-coupling reactions of aryl halides with furyl metal reagents or furyl halides with aryl metal reagents were also reported.[3] During the past years, the direct C-H bond functionalization of aryl (pseudo)halides with heteroaromatic compounds, which at least avoids pre-functionalization in one of the starting materials, has attracted much attention for the functionalization of hetereoaromatic compounds.[4] Despite the great growth in such area, however, the direct C-H bond arylation of benzo[*b*]furans seems to be ignored. It was reported that compared to other five-membered heteroaromatic compounds such as furans and (benzo)thiophenes, the C2-C3 bond on benzo[*b*]furans seems more like a localized olefinic double bond rather than an aromatic system.[5] As a result, the sole direct C-H bond arylation of benzo[*b*]furans on the C2 or C3 position became more challenge, usually giving the mixture of C2, C3 and the bi-arylated benzo[*b*]furans in the same system.[6] Due to the above reasons, in sharp contrast to the abundant papers on the direct C-H bond arylation of furans and (benzo)thiophenes,[7] only a handful of examples on the direct C-H bond arylation of benzo[*b*]furans was reported to date by Ohta,[8] Correia,[9] DeBoef,[10] Schnürch,[11] and others.[12] For example, Ohta[8] and Schnürch[11] used the active aryl bromides as the arylating reagents in such transformation. Aryldiazonium salts were used as the arylating reagents in Correia's method.[9] DeBoef developed the most desirable C-H bond arylation of benzo[*b*]furans using arenes as the arylating reagents.[10] However, some problems, such as lack of regioselectivity, large excess of arenes required, and at least a stoichiometric oxidant necessary, decreased the efficiency of such methodology. In addition, examples on the direct C-H bond arylation of benzo[*b*]furans with chlorobenzene via benzyne intermediate were also reported by Daugulis.[13] However, because of the high activity of the benzyne intermediate, the regioselectivity was the fatal shortcoming, and no other aryl chlorides were tested in Daugulis' works. Therefore, to the best of our knowledge, the direct C-H bond arylation of

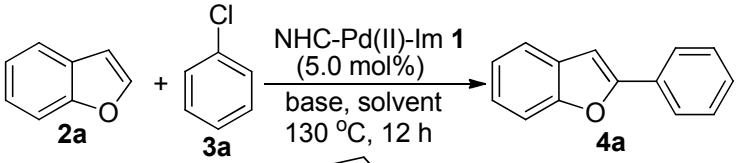
benzo[*b*]furans on the C2 position with sole selectivity, especially using the inexpensive and easily available while less active aryl chlorides as the arylating reagents, was far from well developed.

In 2011, a well-defined *N*-heterocyclic carbene-palladium(II)-1-methylimidazole [NHC-Pd(II)-Im] complex **1** was developed by our group, and during the past years, it has been proven a good catalyst in activating aryl chlorides toward C-C and C-N coupling reactions.[14] Furthermore, it was also found to be an efficient catalyst in the direct C-H bond arylation of (benzo)oxazoles, (benz)imidazoles and fluorenes with aryl chlorides.[15] Based on the previous studies, it can be postulated that the highly active NHC-Pd(II)-Im complex may be an efficient catalyst to activate aryl chlorides toward the direct sole C2-H bond arylation of benzo[*b*]furans. Therefore, prompted by our successful experiences on the above reactions, we then turned our interest to the challengingly direct C-H bond arylation of benzo[*b*]furans with aryl chlorides in sole C2-selectivity. Herein, we report our efforts on the direct C2-H bond arylation of various benzo[*b*]furans with kinds of (hetero)aryl chlorides catalyzed by NHC-Pd(II)-Im complex **1** in detail.

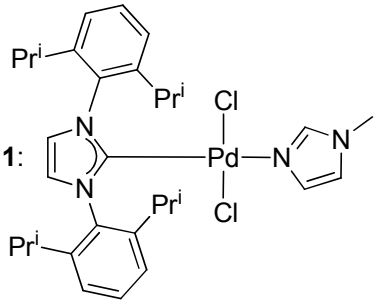
The reaction conditions were first optimized by using the model reaction of benzo[*b*]furan **2a** (1.0 mmol) with chlorobenzene **3a** (0.5 mmol) in the presence of NHC-Pd(II)-Im complex **1** (5.0 mol%) in toluene (2.0 mL) at 130 ^{o}C for 12 h to evaluate various bases (2.5 equiv). Some representative results are shown in Table 1. Among the bases screened (Table 1, entries 1-4), KO^{t}Bu gave the best yield of 42% (Table 1, entry 1). In the presence of other bases such as NaO^{t}Bu, NaOH and KOH, very low yields of the corresponding product **4a** were observed (Table 1, entries 2-4). In addition, no reaction occurred using other bases such as LiO^{t}Bu, Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, $K_3PO_4{\cdot}3H_2O$, $NaHCO_3$ and KOAc. The yield remained unchanged using KO^{t}Bu as the base even if the reaction time was prolonged to 24 h. When the amount of KO^{t}Bu was decreased to 1.2 equiv, similar yield of product **4a** was observed (Table 1, entry 5 *vs* entry 1), while that of KO^{t}Bu was further decreased to 1.0 equiv, the yield slightly decreased to 37% (Table 1, entry 6 *vs* entry 1). Then a variety of solvents was tested in the presence of 1.2 equiv KO^{t}Bu. For example, when THF was chosen as the solvent, product **4a** was obtained in 52%

yield (Table 1, entry 7). However, using other solvents such as DMSO, CH_3CN and DMF, no reaction occurred. Considering that in the transition metal catalyzed direct C-H bond functionalization of heteroaromatic compounds, additives are usually proposed to enhance the reactions to some extent. Therefore, a series of copper salts was first examined, and it was found that copper salts can indeed affect the reaction (Table 1, entries 8-14). For example, all copper salts besides CuBr can promote this reaction to give higher yields, and the best result was achieved using Cu_2O as the additive (Table 1, entry 11).[16] It was noted here that the best 77% yield may be due to the incomplete conversion. For example, only the starting benzo[*b*]furan **2a** and product **4a** were detected by GC-MS, implying that no side reaction occurred. In addition, the yield almost kept untouched even if the reaction time was prolonged to 18 h. In addition, compared to Cu_2O, inferior results were observed using other additives such as PivOH (48%), PivONa (51%), AgOAc (44%) and Ag_2CO_3 (43%).[17] Using Cu_2O (10.0 mol%) as the catalyst in the absence of NHC-Pd(II)-Im complex **1**, no reaction occurred. Finally, it is worthy of noting here that in all the above reactions, only the C2-arylated product **4a** was obtained, and no C3-arylated by-product was detected in any cases.

Table 1. Optimization for the Complex **1** Catalyzed Reaction of Benzo[*b*]furan **2a** with Chlorobenzene **3a**.



NHC-Pd(II)-Im **1**:



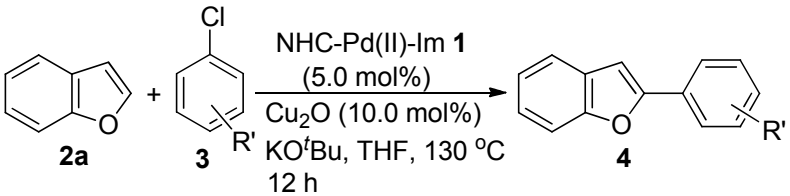
entry[a]	base (equiv)	solvent	additive	yield (%)
1	KO^{t}Bu (2.5)	toulene	—	42
2	NaO^{t}Bu (2.5)	toulene	—	<5
3	NaOH (2.5)	toulene	—	<5
4	KOH (2.5)	toulene	—	7
5	KO^{t}Bu (1.2)	toulene	—	44
6	KO^{t}Bu (1.0)	toulene	—	37
7	KO^{t}Bu (1.2)	THF	—	52
8	KO^{t}Bu (1.2)	THF	CuCl	64
9	KO^{t}Bu (1.2)	THF	CuI	69
10	KO^{t}Bu (1.2)	THF	CuBr	50
11	**KO^{t}Bu (1.2)**	**THF**	**Cu_2O**	**77**
12	KO^{t}Bu (1.2)	THF	CuO	69
13	KO^{t}Bu (1.2)	THF	$CuBr_2$	58
14	KO^{t}Bu (1.2)	THF	$Cu(OAc)_2$	58

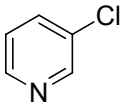
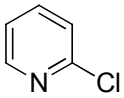
[a]All reactions were carried out using **2a** (1.0 mmol), **3a** (0.5 mmol), **1** (5.0 mol%), additive (0 or 10.0 mol%), base (1.0-2.5 equiv) in solvent (2.0 mL) at 130 °C for 12 h.

With the optimal conditions established, the scope and limitation of this reaction was first examined by using a number of aryl chlorides **3** and benzo[*b*]furan **2a** (Table 2). As can be seen from Table 2, substituents on the aryl chlorides **3** had some effect on the reactions. For example, aryl chlorides **3** having electron-donating substituents such as methoxy and methyl groups were better substrates than that having electron-withdrawing group such as fluorine atom, giving superior yields under identical conditions (Table 2, entries 1-6 *vs* 7 and 8). Sterically hindered substituents on the aryl chlorides **3** did

not affect the reactions significantly to give the corresponding products **4d** and **4g** in good yields, respectively (Table 2, entries 3 and 6). The vinyl group on the aryl chloride **3j** kept untouched in such transformation to give the desired arylated product **4j** in 75% yield (Table 2, entry 9). Heteroaryl chlorides such as 3-chloropyridine **3k** and its analogue, 2-chloropyridine **3l**, were also suitable substrates in the presence of elevated amount of KO^{t}Bu (2.5 equiv) to give the corresponding products **4k** and **4l** in 77% and 54% yields, respectively (Table 2, entries 11 and 13).

Table 2. NHC-Pd(II)-Im Complex **1** Catalyzed Reactions of Benzo[*b*]furan **2a** with Aryl Chlorides **3**.

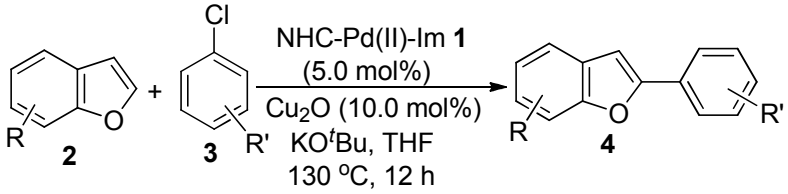


entry[a]	**3** (R')	yield (%)
1	**3b** (4-OMe)	**4b**, 81
2	**3c** (3-OMe)	**4c**, 78
3	**3d** (2-OMe)	**4d**, 76
4	**3e** (4-Me)	**4e**, 74
5	**3f** (3-Me)	**4f**, 77
6	**3g** (2-Me)	**4g**, 69
7	**3h** (4-F)	**4h**, 65
8	**3i** (3-F)	**4i**, 60
9	**3j** (4-vinyl)	**4j**, 75
10	**3k** 	**4k**, 47
11[b]	**3k**	**4k**, 77
12	**3l** 	**4l**, 36
13[b]	**3l**	**4l**, 54

[a]Otherwise specified, all reactions were carried out using **2a** (1.0 mmol), **3** (0.5 mmol), **1** (5.0 mol%), Cu_2O (10.0 mol%), KO^{t}Bu (1.2 equiv) in THF (2.0 mL) at 130 °C for 12 h.
[b]KO^{t}Bu (2.5 equiv) was added.

Encouraged by the above successful results, the reactions of a variety of benzo[*b*]furans **2** with aryl chlorides **3** were then investigated under the optimal conditions (Table 3). All reactions worked smoothly to give the desired C2-arylated products **4** in moderate to good yields. Substituents such as electron-donating, -withdrawing and sterically hindered ones on both substrates did not affect the reactions significantly. For instance, both 7-methylbenzo[*b*]furan **2c** and 7-fluorobenzo[*b*]furan **2e** having sterically hindered substituent were suitable substrates to give the desired C2-arylated products in moderate to good yields (Table 3, entries 7-11, 14 and 15). Sterically hindered 2-methylphenyl chloride **3g** was also a good substrate to afford the corresponding products **4p** and **4v** in 75% and 72% yields, respectively (Table 3, entries 4 and 10). The reaction involving strongly electron-withdrawing 5-CF_3 substituted **2f** also worked well to give product **4ab** in 69% yield (Table 3, entry 16).

Table 3. NHC-Pd(II)-Im Complex **1** Catalyzed Reactions of Benzo[*b*]furans **2** with Aryl Chlorides **3**.



entry[a]	**2** (R)	**3** (R')	yield (%)
1	**2b** (5-Me)	**3a** (H)	**4m**, 83
2	**2b**	**3e** (4-Me)	**4n**, 76
3	**2b**	**3f** (3-Me)	**4o**, 72
4	**2b**	**3g** (2-Me)	**4p**, 75
5	**2b**	**3h** (4-F)	**4q**, 71
6	**2b**	**3j** (4-vinyl)	**4r**, 80
7	**2c** (7-Me)	**3a**	**4s**, 73
8	**2c**	**3e**	**4t**, 80
9	**2c**	**3f**	**4u**, 73
10	**2c**	**3g**	**4v**, 72
11	**2c**	**3j**	**4w**, 68
12	**2d** (5-F)	**3a**	**4x**, 76
13	**2d**	**3b** (4-OMe)	**4y**, 82
14	**2e** (7-F)	**3a**	**4z**, 62
15	**2e**	**3e**	**4aa**, 83
16	**2f** (5-CF_3)	**3e**	**4ab**, 69

[a]All reactions were carried out using **2** (1.0 mmol), **3** (0.5 mmol), **1** (5.0 mol%), Cu_2O (10.0 mol%), KO^{t}Bu (1.2 equiv) in THF (2.0 mL) at 130 °C for 12 h.

In conclusion, the first example of NHC-Pd(II) complex catalyzed sole direct C2-H bond arylation of benzo[*b*]furans with aryl chlorides was reported in this paper. Under the optimal conditions, various benzo[*b*]furans can be arylated solely in the C2-position with (hetero)aryl chlorides catalyzed by NHC-Pd(II)-Im complex **1**. In addition, various substituents such as electron-donating, -neutral, -withdrawing and sterically hindered ones on both substrates can be tolerated, affording a novel and efficient methodology for the direct C2-H bond arylation of benzo[*b*]furans with economic and easily available aryl chlorides.

Experimental section

General Remarks. Melting points are uncorrected. NMR spectra were recorded at 500 (for ^{1}H NMR) or 125 MHz (for ^{13}C NMR), respectively. ^{1}H NMR and ^{13}C NMR spectra recorded in $CDCl_3$ solutions were referenced to TMS (0.00 ppm) and the residual solvent peak (77.0 ppm), respectively. *J*-values are in Hz. Organic solvents used were dried by standard methods. The mass analyzer type for the high resolution mass spectra (HRMS, ESI) is quadrupole. Other commercially obtained reagents were used without further purification. Flash column chromatography was performed on silica gel.

General Procedure for the NHC-Pd(II)-Im Complex 1 Catalyzed Direct C-H Bond Arylation of Benzo[b]furans 2 with Aryl Chlorides 3. Under N_2 atmosphere, KO^{t}Bu (67.3 mg, 0.6 mmol, 1.2 equiv), Cu_2O (7.2 mg, 0.05 mmol, 10.0 mol%), NHC-Pd(II)-Im complex **1** (16.0 mg, 0.025 mmol, 5.0 mol%), THF (2.0 mL), benzo[*b*]furans **2** (2.0 equiv) and aryl chlorides **3** (0.5 mmol) were successively added into a sealed tube. The mixture was stirred vigorously at 130 ^{o}C for 12 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (eluent: petroleum ether) to give the pure products **4**.

Compound **4a**: white solid (74.7 mg, 77%); mp: 120-121 ^{o}C (lit.[18] 120-121 ^{o}C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.87 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.37-7.34 (m, 1H), 7.28 (td, *J* = 8.0, 1.0 Hz, 1H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 7.03 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.5, 124.9, 124.2, 122.9, 120.9, 111.2, 101.3.

Compound **4b**: white solid (90.8 mg, 81%); mp: 148-149 ^{o}C (lit.[2p] 148-150 ^{o}C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.80 (dt, *J* = 9.5, 3.0 Hz, 2H), 7.56-7.54 (m, 1H), 7.51-7.49 (m, 1H), 7.25 (td, *J* = 8.5, 1.5 Hz, 1H), 7.21 (td, *J* = 7.0, 1.0 Hz, 1H), 6.98 (dt, *J* = 5.0, 2.0 Hz, 2H), 6.88 (d, *J* = 0.5 Hz, 1H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 160.0, 156.1, 154.7, 129.5, 126.4, 123.7, 123.4, 122.8, 120.6, 114.3, 111.0, 99.7, 55.4.

Compound **4c**: white solid (87.4 mg, 78%); mp: 51-52 ^{o}C (lit.[19] 51-53 ^{o}C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.41 (t, *J*

= 2.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.28 (td, *J* = 8.0, 1.0 Hz, 1H), 7.22 (td, *J* = 8.0, 1.0 Hz, 1H), 7.01 (d, *J* = 0.5 Hz, 1H), 6.90 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H), 3.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 160.0, 155.8, 154.9, 131.8, 129.8, 129.2, 124.3, 122.9, 120.9, 117.6, 114.5, 111.2, 110.2, 101.6, 55.3.

Compound **4d**: white solid (85.2 mg, 76%); mp: 79-80 °C (lit.[20] 79-80 °C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.30-7.24 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 156.5, 153.9, 152.2, 129.8, 129.2, 127.1, 124.1, 122.6, 121.0, 120.8, 119.4, 111.1, 110.8, 106.3, 55.4.

Compound **4e**: white solid (77.0 mg, 74%); mp: 128-129 °C (lit.[21] 128-129 °C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.27-7.19 (m, 4H), 6.93 (s, 1H), 2.37 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 156.2, 154.8, 138.5, 129.44, 129.37, 127.8, 124.9, 124.0, 122.8, 120.7, 111.1, 100.5, 21.3.

Compound **4f**: white solid (80.1 mg, 77%); mp: 75-76 °C (lit.[2p] 74-75 °C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.67 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.31-7.19 (m, 3H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.96 (s, 1H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 156.1, 154.9, 138.4, 130.4, 129.4, 129.3, 128.7, 125.5, 124.2, 122.9, 122.2, 120.8, 111.1, 101.2, 21.5.

Compound **4g**[3d]: colorless liquid (71.8 mg, 69%); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.83 (d, *J* = 7.0 Hz, 1H), 7.57 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 4H), 7.21 (td, *J* = 7.5, 0.5 Hz, 1H), 6.85 (s, 1H), 2.55 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 155.6, 154.4, 135.8, 131.2, 129.9, 129.2, 128.5, 128.1, 126.1, 124.2, 122.8, 120.9, 111.1, 105.1, 21.9.

Compound **4h**: white solid (68.9 mg, 65%); mp: 120-121 °C (lit.[2p] 120-122 °C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.84-7.81 (m, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 8.5 Hz, 2H), 6.94 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125

MHz) δ 162.9 (d, J_{C-F} = 247.25 Hz), 155.0 (d, J_{C-F} = 19.75 Hz), 129.2, 126.8 (d, J = 8.125 Hz), 124.3, 123.0, 120.9, 115.9 (d, J_{C-F} = 21.875 Hz), 111.1, 101.0 (d, J = 1.5 Hz).

Compound **4i**: white solid (63.6 mg, 60%); mp: 77-78 °C (lit.[20] 77-78 °C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.61 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.54 (dt, J =10.0, 2.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.38 (td, J = 8.0, 6.0 Hz, 1H), 7.29 (td, J = 8.0, 1.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.04-7.00 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 163.2 (d, J_{C-F} = 244.25 Hz), 154.9, 154.6 (d, J = 3.0 Hz), 132.6 (d, J = 8.375 Hz), 130.4 (d, J = 8.375 Hz), 129.0, 124.7, 123.1, 121.1, 120.6 (d, J = 2.875 Hz), 115.3 (d, J = 21.25 Hz), 111.8 (d, J = 23.375 Hz), 111.2, 102.3.

Compound **4j**: white solid (82.5 mg, 75%); mp: 168-169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.80 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.26 (td, J = 8.0, 1.0 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 6.98 (s, 1H), 6.72 (dd, J = 18.0, 10.5 Hz, 1H), 5.79 (d, J = 18.0 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.7, 154.9, 137.7, 136.3, 129.7, 129.2, 126.6, 125.0, 124.3, 122.9, 120.9, 114.4, 111.1, 101.4; MS (ESI): 221 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{13}O$ $[M+H]^+$: 221.0961; found: 221.0952; IR (neat) ν 3044, 1624, 1604, 1576, 1497, 1450, 1407, 1348, 1259, 1166, 1112, 1104, 1034, 1011, 990, 930, 906, 882, 845, 803, 747, 738 cm^{-1}.

Compound **4k**[22]: yellow solid (75.1 mg, 77%); mp: 79-80 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 9.10 (s, 1H), 8.56 (dd, J = 4.5, 1.0 Hz, 1H), 8.10-8.07 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.35-7.29 (m, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.1, 152.9, 149.2, 146.4, 131.8, 128.7, 126.6, 124.9, 123.5, 123.2, 121.1, 111.2, 102.7.

Compound **4l**: yellow solid (52.7 mg, 54%); mp: 84-85 °C (lit.[23] 80-81 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 4.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.27-7.21 (m, 2H); ^{13}C{^{1}H} NMR

($CDCl_3$, 125 MHz) δ 155.3, 155.1, 149.9, 149.3, 136.7, 128.9, 125.2, 123.2, 122.8, 121.7, 119.8, 111.5, 104.8.

Compound **4m**: white solid (86.3 mg, 83%); mp: 129-130 °C (lit.[2p] 131-133 °C); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.83 (d, *J* = 7.5 Hz, 2H), 7.43-7.37 (m, 3H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 156.0, 153.4, 132.3, 130.7, 129.3, 128.7, 128.4, 125.5, 124.9, 120.7, 110.6, 101.1, 21.3.

Compound **4n**: white solid (84.4 mg, 76%); mp: 140-141 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.33 (s, 1H), 7.24-7.22 (m, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.87 (s, 1H), 2.43 (s, 3H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 156.3, 153.3, 138.4, 132.2, 129.47, 129.44, 128.0, 125.2, 124.8, 120.6, 110.6, 100.3, 21.32, 21.30; MS (ESI): 223 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O$ $[M+H]^+$: 223.1117; found: 223.1122; IR (neat) ν 3014, 2908, 2842, 1501, 1461, 1375, 1328, 1275, 1262, 1209, 1196, 1133, 1113, 1036, 1013, 914, 879, 821, 798, 743 cm^{-1}.

Compound **4o**: white solid (80.0 mg, 72%); mp: 78-79 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.67 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.34 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.92 (s, 1H), 2.43 (s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 156.2, 153.4, 138.4, 132.3, 130.6, 129.4, 129.2, 128.7, 125.5, 125.4, 122.1, 120.7, 110.6, 101.0, 21.5, 21.3; MS (ESI): 223 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O$ $[M+H]^+$: 223.1117; found: 223.1113; IR (neat) ν 2928, 2855, 1610, 1560, 1457, 1328, 1265, 1199, 1133, 1050, 925, 884, 853, 814, 801, 783, 740, 692 cm^{-1}.

Compound **4p**: colorless liquid (83.3 mg, 75%); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.82 (d, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.29-7.22 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 2.54 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.7, 152.8, 135.7, 132.1, 131.2, 130.0, 129.3, 128.3, 128.0, 126.0, 125.5, 120.7, 110.5, 104.8, 21.9, 21.3. MS (ESI): 223 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O$ $[M+H]^+$: 223.1117; found: 223.1115; IR (neat) ν 3014, 2961, 2921, 2855, 1618, 1601, 1590, 1573, 1472, 1461, 1379, 1329, 1270, 1194, 1129, 1020, 914, 869, 830, 799, 760, 738, 719 cm^{-1}.

Compound **4q**[2r]: white solid (80.3 mg, 71%); mp: 161-162 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.82-7.78 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.14-7.07 (m, 3H), 6.86 (s, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 162.8 (d, J_{C-F} = 247.0 Hz), 155.1, 153.3, 132.4, 129.3, 127.0 (d, J_{C-F} = 3.125 Hz), 126.7 (d, J_{C-F} = 8.125 Hz), 125.5, 120.7, 115.8 (d, J_{C-F} = 21.875 Hz), 110.6, 100.8 (d, J = 1.625 Hz), 21.3.

Compound **4r**: white solid (93.6 mg, 80%); mp: 168-169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.77 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.31 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 6.71 (dd, J = 18.0, 10.5 Hz, 1H), 5.78 (d, J = 18.0 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.7, 153.3, 137.6, 136.3, 132.3, 129.9, 129.3, 126.6, 125.6, 124.9, 120.7, 114.3, 110.6, 101.2, 21.3; MS (ESI): 235 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{15}O$ $[M+H]^+$: 235.1117; found: 235.1124; IR (neat) ν 3083, 2920, 2847, 1627, 1607, 1582, 1506, 1464, 1405, 1379, 1334, 1261, 1197, 1115, 1039, 989, 913, 900, 845, 802, 741 cm^{-1}.

Compound **4s**[24]: colorless liquid (75.9 mg, 73%); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.84 (d, J = 7.5 Hz, 2H), 7.41-7.36 (m, 3H), 7.30 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.95 (s, 1H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.5, 153.9, 130.7, 128.70, 128.65, 128.4, 125.2, 124.8, 122.9, 121.4, 118.3, 101.6, 15.0.

Compound **4t**: colorless liquid (88.8 mg, 80%); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.73 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.0 Hz, 1H), 6.89 (s, 1H), 2.56 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 155.8, 153.8, 138.4, 129.4, 128.8, 128.0, 124.9, 124.8, 122.9, 121.3, 118.2, 100.8, 21.3, 15.0; MS (ESI): 223 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O$ $[M+H]^+$: 223.1117; found: 223.1110; IR (neat) ν 3055, 3021, 2914, 1506, 1483, 1452, 1416, 1351, 1292, 1202, 1174, 1160, 1031, 1014, 911, 857, 821, 809, 802, 765, 741 cm^{-1}.

Compound **4u**: colorless liquid (81.0 mg, 73%); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.68-7.65 (m, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H),

7.06 (d, J = 7.5 Hz, 1H), 6.96 (s, 1H), 2.58 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 155.7, 153.9, 138.3, 130.6, 129.2, 128.7, 128.6, 125.4, 125.1, 122.9, 122.1, 121.3, 118.3, 101.4, 21.5, 15.0; MS (ESI): 223 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O$ $[M+H]^+$: 223.1117; found: 223.1116; IR (neat) ν 3057, 2917, 2852, 1612, 1574, 1484, 1451, 1414, 1349, 1291, 1214, 1186, 1091, 1040, 928, 864 cm^{-1}.

Compound **4v**: colorless liquid (79.9 mg, 72%); ^1H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.83 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.29-7.23 (m, 3H), 7.12 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 7.0 Hz, 1H), 6.85 (s, 1H), 2.564 (s, 3H), 2.559 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 155.4, 153.5, 135.8, 131.3, 130.1, 128.6, 128.4, 128.1, 126.0, 125.1, 122.8, 121.3, 118.3, 105.2, 21.9, 15.0; MS (ESI): 223 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{15}O$ $[M+H]^+$: 223.1117; found: 223.1121; IR (neat) ν 3067, 2915, 2855, 1484, 1457, 1418, 1381, 1295, 1209, 1179, 1020, 911, 856, 806, 768, 743, 717 cm^{-1}.

Compound **4w**: white solid (79.6 mg, 68%); mp: 88-89 °C; ^1H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.78 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.94 (s, 1H), 6.71 (dd, J = 17.5, 11.0 Hz, 1H), 5.77 (d, J = 17.5 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 155.3, 153.9, 137.6, 136.3, 130.0, 128.7, 126.6, 125.2, 125.0, 123.0, 121.4, 118.3, 114.3, 101.7, 15.0; MS (ESI): 235 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{15}O$ $[M+H]^+$: 235.1117; found: 235.1127; IR (neat) ν 2920, 2847, 1697, 1621, 1607, 1582, 1500, 1486, 1407, 1351, 1295, 1264, 1205, 1180, 1031, 1008, 990, 913, 845, 812, 771, 743 cm^{-1}.

Compound **4x**: white solid (80.6 mg, 76%); mp: 130-131 °C; ^1H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.81 (d, J = 7.0 Hz, 2H), 7.43-7.38 (m, 3H), 7.34 (t, J = 7.5 Hz, 1H), 7.19 (dd, J = 8.5, 2.5 Hz, 1H), 6.97 (td, J = 9.0, 2.5 Hz, 1H), 6.92 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 159.3 (d, $J_{C\text{-}F}$ = 236.5 Hz), 157.7, 151.1, 130.1 (d, $J_{C\text{-}F}$ = 8.25 Hz), 129.9, 128.8 (d, J = 7.375 Hz), 125.0, 111.8 (d, $J_{C\text{-}F}$ = 24.375 Hz); 111.7 (d, $J_{C\text{-}F}$ = 7.625 Hz); 106.3 (d, $J_{C\text{-}F}$ = 25.0 Hz), 101.4 (d, J = 4.0 Hz); MS (ESI): 213 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{10}FO$ $[M+H]^+$: 213.0710; found: 213.0699; IR (neat) ν 3100, 3065, 3040, 2914, 2847, 1593, 1457, 1441, 1341, 1272, 1189, 1129, 1020, 950, 915, 866, 799, 762, 741 cm^{-1}.

Compound **4y**: white solid (99.2 mg, 82%); mp: 145-146 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.75 (d, *J* = 9.0 Hz, 2H), 7.38 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.17 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.96-6.92 (m, 3H), 6.80 (d, *J* = 0.5 Hz, 1H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 160.2, 159.3 (d, J_{C-F} = 236.125 Hz), 157.9, 150.9, 130.3 (d, *J* = 10.875 Hz), 126.5, 123.0, 114.3, 111.4 (d, J_{C-F} = 9.625 Hz), 111.2 (d, J_{C-F} = 26.25 Hz), 106.0 (d, J_{C-F} = 25.0 Hz), 99.8 (d, J_{C-F} = 3.875 Hz), 55.3; MS (ESI): 243 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{12}FO_2$ $[M+H]^+$: 243.0816; found: 243.0819; IR (neat) ν 3014, 2968, 2835, 1610, 1587, 1567, 1504, 1457, 1418, 1348, 1305, 1245, 1169, 1123, 1109, 1036, 1023, 954, 914, 864, 829, 819, 809, 790, 763, 738 cm^{-1}.

Compound **4z**: white solid (65.7 mg, 62%); mp: 65-66 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.12 (td, *J* = 7.5, 4.0 Hz, 1H), 7.02-6.98 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 157.0, 148.0 (d, J_{C-F} = 247.75 Hz), 141.8 (d, *J* = 11.125 Hz), 132.7 (d, *J* = 3.375 Hz), 129.8, 128.9 (d, *J* = 17.0 Hz), 125.1, 123.5 (d, *J* = 5.875 Hz), 116.5 (d, *J* = 3.75 Hz), 110.6 (d, *J* = 16.125 Hz), 101.5 (d, *J* = 2.25 Hz); MS (ESI): 213 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{10}FO$ $[M+H]^+$: 213.0710; found: 213.0713; IR (neat) ν 3106, 3055, 2926, 1632, 1590, 1495, 1481, 1433, 1306, 1259, 1216, 1180, 1056, 1045, 1017, 909, 879, 861, 816, 769, 755, 723 cm^{-1}.

Compound **4aa**: white solid (93.8 mg, 83%); mp: 119-120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.09 (td, *J* = 8.0, 4.5 Hz, 1H), 6.97 (dd, *J* = 10.5, 8.0 Hz, 1H), 6.90 (d, *J* = 3.0 Hz, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 157.3, 148.0 (d, J_{C-F} = 247.375 Hz), 141.6 (d, J_{C-F} = 10.875 Hz), 139.0, 132.9 (d, J_{C-F} = 3.25 Hz), 129.5, 127.1, 125.0, 123.4 (d, J_{C-F} = 5.875 Hz), 116.3 (d, J_{C-F} = 3.75 Hz), 110.3 (d, J_{C-F} = 16.125 Hz), 100.7 (d, J_{C-F} = 2.0 Hz), 21.3; MS (ESI): 227 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{12}FO$ $[M+H]^+$: 227.0867; found: 227.0866; IR (neat) ν 2915, 2868, 1630, 1597, 1507, 1484, 1434, 1328, 1308, 1259, 1212, 1179, 1056, 1043, 909, 864, 848, 806, 770, 723 cm^{-1}.

Compound **4ab**: white solid (95.3 mg, 69%); mp: 153-154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.83 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.97 (s, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 158.2, 156.1, 139.4, 129.6, 128.2 (q, $J_{C\text{-}F}$ = 303.75 Hz), 125.8, 125.6 (q, $J_{C\text{-}F}$ = 32.0 Hz), 123.6, 121.0 (q, $J_{C\text{-}F}$ = 3.5 Hz), 118.3 (q, $J_{C\text{-}F}$ = 3.875 Hz), 111.8, 111.4, 104.4, 100.5, 21.4; MS (ESI): 277 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{12}F_3O$ $[M+H]^+$: 277.0835; found: 227.0848; IR (neat) ν 3027, 2921, 2862, 1613, 1583, 1504, 1441, 1331, 1278, 1259, 1156, 1113, 1053, 927, 909, 891, 821, 791, 751 cm^{-1}.

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Supporting Information Available. Copy of ^{1}H and ^{13}C NMR spectra of compounds **4**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Graphic abstract