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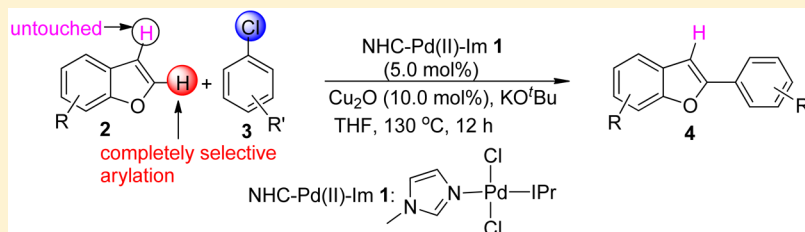
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N-Heterocyclic Carbene-Palladium(II)-1-Methylimidazole Complex Catalyzed Direct C–H Bond Arylation of Benzo[*b*]furans with Aryl Chlorides

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S Supporting Information



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.

The 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 an 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 prefunctionalization in one of the starting materials, has attracted much attention for the functionalization of heteroaromatic 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 of a challenge, usually giving the mixture of C2, C3 and the biarylated 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, Ohta⁸ and Schnürch¹¹ 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

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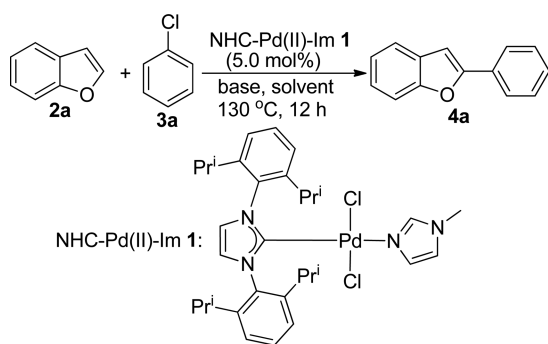
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direct sole C2–H bond arylation of benzo[*b*]furans. Therefore, prompted by our successful experiences on the above reactions, we then turned our interest to the challengingly direct C–H bond arylation of benzo[*b*]furans with aryl chlorides in sole 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 °C for 12 h to evaluate various bases (2.5 equiv). Some representative results are shown in Table 1. Among the bases

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



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 ₂ O	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

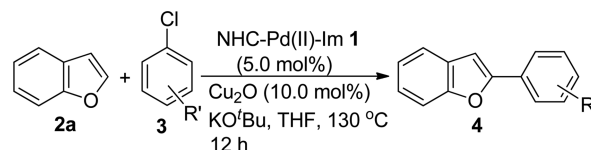
^aAll reactions were carried out using **2a** (1.0 mmol), **3a** (0.5 mmol), **1** (5.0 mol %), additive (0 or 10.0 mol %), base (1.0–2.5 equiv) in solvent (2.0 mL) at 130 °C for 12 h.

screened (Table 1, entries 1–4), KO^tBu gave the best yield of 42% (Table 1, entry 1). In the presence of other bases such as NaO^tBu, 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^tBu, Li₂CO₃, Na₂CO₃, K₂CO₃, Cs₂CO₃, K₃PO₄·3H₂O, NaHCO₃, and KOAc. The yield remained unchanged using KO^tBu as the base even if the reaction time was prolonged to 24 h. When the amount of KO^tBu was decreased to 1.2 equiv, similar yield of product **4a** was observed (Table 1, entry 5 vs entry 1), while that of KO^tBu 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^tBu. 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, CH₃CN, and DMF, no reaction occurred. Considering that in the transition-metal-catalyzed direct C–H bond functionalization of hetero-aromatic 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 Cu₂O 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 Cu₂O, inferior results were observed using other additives such as PivOH (48%), PivONa (51%), AgOAc (44%), and Ag₂CO₃ (43%).¹⁷ Using Cu₂O (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 byproduct was detected in any cases.

With the optimal conditions established, the scope and limitation of this reaction were 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 those having an

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 (4-Cl)	4k , 47
11 ^b	3k (3-Cl)	4k , 77
12	3l (2-Cl)	4l , 36
13 ^b	3l (4-Cl)	4l , 54

^aOtherwise specified, all reactions were carried out using **2a** (1.0 mmol), **3** (0.5 mmol), **1** (5.0 mol %), Cu₂O (10.0 mol %), KO^tBu (1.2 equiv) in THF (2.0 mL) at 130 °C for 12 h. ^bKO^tBu (2.5 equiv) was added.

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^tBu (2.5 equiv) to give the corresponding products 4k and 4l in 77% and 54% yields, respectively (Table 2, entries 11 and 13).

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

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

^aAll reactions were carried out using 2 (1.0 mmol), 3 (0.5 mmol), 1 (5.0 mol %), Cu₂O (10.0 mol %), KO^tBu (1.2 equiv) in THF (2.0 mL) at 130 °C for 12 h.

reactions worked smoothly to give the desired C2-arylated products 4 in moderate to good yields. Substituents such as electron-donating and -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-CF₃ substituted 2f also worked well to give product 4ab in 69% yield (Table 3, entry 16).

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, and -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 ¹H NMR) or 125 MHz (for ¹³C NMR), respectively. ¹H NMR and ¹³C NMR spectra recorded in CDCl₃ 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 N₂ atmosphere, KO^tBu (67.3 mg, 0.6 mmol, 1.2 equiv), Cu₂O (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 °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 °C (lit.¹⁸ 120–121 °C); ¹H NMR (CDCl₃, 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); ¹³C{¹H} NMR (CDCl₃, 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 °C (lit.^{2p} 148–150 °C); ¹H NMR (CDCl₃, 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); ¹³C{¹H} NMR (CDCl₃, 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 °C (lit.¹⁹ 51–53 °C); ¹H NMR (CDCl₃, 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); ¹³C{¹H} NMR (CDCl₃, 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); ¹H NMR (CDCl₃, 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); ¹³C{¹H} NMR (CDCl₃, 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); ¹H NMR (CDCl₃, 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); ¹³C{¹H} NMR (CDCl₃, 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); ¹H NMR (CDCl₃, 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); $^{13}\text{C}\{^1\text{H}\}$ 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%); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 162.9 (d, $J_{\text{C-F}}$ = 247.25 Hz), 155.0 (d, $J_{\text{C-F}}$ = 19.75 Hz), 129.2, 126.8 (d, J = 8.125 Hz), 124.3, 123.0, 120.9, 115.9 (d, $J_{\text{C-F}}$ = 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.^{2o} 77–78 °C); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 163.2 (d, $J_{\text{C-F}}$ = 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; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{13}\text{O}$ $[\text{M} + \text{H}]^+$: 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; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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); ^1H NMR (500 MHz, CDCl_3 , TMS) 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); $^{13}\text{C}\{^1\text{H}\}$ 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); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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%); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 162.8 (d, $J_{\text{C-F}}$ = 247.0 Hz), 155.1, 153.3, 132.4, 129.3, 127.0 (d, $J_{\text{C-F}}$ = 3.125 Hz), 126.7 (d, $J_{\text{C-F}}$ = 8.125 Hz), 125.5, 120.7, 115.8 (d, $J_{\text{C-F}}$ = 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; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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%); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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%); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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%); ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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); $^{13}\text{C}\{^1\text{H}\}$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{O}$ $[\text{M} + \text{H}]^+$: 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 $^\circ\text{C}$; ^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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 159.3 (d, $J_{\text{C-F}} = 236.5$ Hz), 157.7, 151.1, 130.1 (d, $J_{\text{C-F}} = 8.25$ Hz), 129.9, 128.8 (d, $J = 7.375$ Hz), 125.0, 111.8 (d, $J_{\text{C-F}} = 24.375$ Hz), 111.7 (d, $J_{\text{C-F}} = 7.625$ Hz), 106.3 (d, $J_{\text{C-F}} = 25.0$ Hz), 101.4 (d, $J = 4.0$ Hz); MS (ESI): 213 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{10}\text{FO}$ $[\text{M} + \text{H}]^+$: 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 $^\circ\text{C}$; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 160.2, 159.3 (d, $J_{\text{C-F}} = 236.125$ Hz), 157.9, 150.9, 130.3 (d, $J = 10.875$ Hz), 126.5, 123.0, 114.3, 111.4 (d, $J_{\text{C-F}} = 9.625$ Hz), 111.2 (d, $J_{\text{C-F}} = 26.25$ Hz), 106.0 (d, $J_{\text{C-F}} = 25.0$ Hz), 99.8 (d, $J_{\text{C-F}} = 3.875$ Hz), 55.3; MS (ESI): 243 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{12}\text{FO}_2$ $[\text{M} + \text{H}]^+$: 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 $^\circ\text{C}$; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 157.0, 148.0 (d, $J_{\text{C-F}} = 247.75$ 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 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{10}\text{FO}$ $[\text{M} + \text{H}]^+$: 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 $^\circ\text{C}$; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 157.3, 148.0 (d, $J_{\text{C-F}} = 247.375$ Hz), 141.6 (d, $J_{\text{C-F}} = 10.875$ Hz), 139.0, 132.9 (d, $J_{\text{C-F}} = 3.25$ Hz), 129.5, 127.1, 125.0, 123.4 (d, $J_{\text{C-F}} = 5.875$ Hz), 116.3 (d, $J_{\text{C-F}} = 3.75$ Hz), 110.3 (d, $J_{\text{C-F}} = 16.125$ Hz), 100.7 (d, $J_{\text{C-F}} = 2.0$ Hz), 21.3; MS (ESI): 227 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{12}\text{FO}$ $[\text{M} + \text{H}]^+$: 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 $^\circ\text{C}$; ^1H 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); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 158.2, 156.1, 139.4, 129.6, 128.2 (q, $J_{\text{C-F}} = 303.75$ Hz), 125.8, 125.6 (q, $J_{\text{C-F}} = 32.0$ Hz), 123.6, 121.0 (q, $J_{\text{C-F}} = 3.5$ Hz), 118.3 (q, $J_{\text{C-F}} = 3.875$ Hz), 111.8, 111.4, 104.4, 100.5, 21.4; MS (ESI): 277 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{O}$ $[\text{M} + \text{H}]^+$: 277.0835; found: 277.0848; IR (neat) ν 3027, 2921, 2862, 1613, 1583, 1504, 1441, 1331, 1278, 1259, 1156, 1113, 1053, 927, 909, 891, 821, 791, 751 cm^{-1} .

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01544.

^1H and ^{13}C NMR spectra of compounds 4 (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For some recent selected papers, please see: (a) Salomé, C.; Ribeiro, N.; Chavagnan, T.; Thuaud, F.; Serova, M.; de Gramont, A.; Faivre, S.; Raymond, E.; Désaubry, L. *Eur. J. Med. Chem.* **2014**, *81*, 181–191. (b) Thévenin, M.; Thoret, S.; Grellier, P.; Dubois, J. *Bioorg. Med. Chem.* **2012**, *21*, 4885–4892. (c) Saha, A. K.; Yu, X.; Lin, J.; Lobera, M.; Sharadendu, A.; Chereku, S.; Schutz, N.; Segai, D.; Marantz, Y.; MacCauley, D.; Middleton, S.; Siu, J.; Bürl, R. W.; Buys, J.; Horner, M.; Salyers, K.; Schrag, M.; Vargas, H. M.; Xu, Y.; McElvain, M.; Xu, H. *ACS Med. Chem. Lett.* **2011**, *2*, 97–101. (d) Xia, Y.; Jin, Y.-L.; Kaur, N.; Choi, Y.; Lee, K. *Eur. J. Med. Chem.* **2011**, *46*, 2386–2396. (e) Bakunov, S. A.; Bakunova, S. M.; Wenzler, T.; Barszcz, T.; Werbovets, K. A.; Brun, R.; Tidwell, R. R. *J. Med. Chem.* **2008**, *51*, 6927–6944.
- (2) For some recent selected papers on the synthesis of 2-aryl benzo[b]furans via cyclization strategy, please see: (a) Mandali, P. K.; Chand, D. K. *Synthesis* **2015**, *47*, 1661–1668. (b) Ruan, L.-B.; Shi, M.; Mao, S.-W.; Yu, L.-F.; Yang, F.; Tang, J. *Tetrahedron* **2014**, *70*, 1065–1070. (c) Sun, S.-X.; Wang, J.-J.; Xu, Z.-J.; Cao, L.-Y.; Shi, Z.-F.; Zhang, H.-L. *Tetrahedron* **2014**, *70*, 3798–3806. (d) Chen, J.-X.; Li, J.-J.; Su, W.-K. *Org. Biomol. Chem.* **2014**, *12*, 4078–4083. (e) Zhou, R.; Wang, W.; Jiang, Z.-J.; Wang, K.; Zheng, X.-L.; Fu, H.-Y.; Chen, H.; Li, R.-X. *Chem. Commun.* **2014**, *50*, 6023–6026. (f) Li, Y.-B.; Cheng, L.; Liu, X.-H.; Li, B.; Sun, N. *Beilstein J. Org. Chem.* **2014**, *10*, 2886–2891. (g) Wang, X.-Y.; Liu, M.-C.; Xu, L.; Wang, Q.-Z.; Chen, J.-X.; Ding, J.-C.; Wu, H.-Y. *J. Org. Chem.* **2013**, *78*, 5273–5181. (h) Siddiqui, I. R.; Waseem, M. A.; Shamim, S.; Srivastava, A. *Tetrahedron Lett.* **2013**, *54*, 4154–4158. (i) Rao, M. L. N.; Jadhav, D. N.; Dasgupta, P. *Eur. J. Org. Chem.* **2013**, *2013*, 781–788. (j) Sharma, U.; Naveen, T.; Maji, A.; Manna, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12669–12673. (k) Cano, R.; Yus, M.; Ramón, D. J. *Tetrahedron* **2012**, *68*, 1393–1400. (l) Ghosh, S.; Das, J.; Saikh, F. *Tetrahedron Lett.* **2012**, *53*, 5883–5886. (m) Liu, J.; Chen, W.; Ji, Y.; Wang, L. *Adv. Synth. Catal.* **2012**, *354*, 1585–1592. (n) Wang, S.-H.; Li, P.-H.; Wang, L. *Org. Lett.* **2011**, *13*, 5968–5971. (o) Boyer, A.; Isono, N.; Lackner, S.; Lautens, M. *Tetrahedron* **2010**, *66*, 6468–6482. (p) Jaseer, E. A.; Prasad, D. J. C.; Sekar, G. *Tetrahedron* **2010**, *66*, 2077–2082. (q) Saha, D.; Dey, R.; Ganu, B. C. *Eur. J. Org. Chem.* **2010**, *2010*, 6067–6071. (r) Geary, L. M.; Hultin, P. G. *Eur. J. Org. Chem.* **2010**, *2010*, 5563–5573. (s) Duan, X.-F.; Feng, J.-X.; Zhang, Z.-B. *Synthesis* **2010**, *2010*, 515–519.
- (3) For some recent selected papers on the transition-metal-catalyzed coupling reactions for the synthesis of 2-aryl benzo[b]furans, please see: (a) Bakouri, O. E.; Fernández, M.; Brun, S.; Pla-Quintana, A.; Roglans, A. *Tetrahedron* **2013**, *69*, 9761–9765. (b) Rao, M. L. N.; Awasthi, D. K.; Talode, J. B. *Tetrahedron Lett.* **2012**, *53*, 2662–2666. (c) Matsuda, S.; Takahashi, M.; Monguchi, D.; Mori, A. *Synlett* **2009**, *2009*, 1941–1944. (d) Denmark, S. E.; Smith, R. C.; Chang, W.-T. T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3104–3118.

(4) For some recent reviews on the direct C–H bond functionalization, please see: (a) Sharma, U.; Modak, A.; Maity, S.; Maji, A.; Maiti, D. Direct arylation via C–H activation. In *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T., Ed.; RSC Catalysis Series: The Royal Society of Chemistry: London, 2015; pp 551–609. (b) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014**, 356, 17–117. (c) Bonin, H.; Sauthier, M.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, 356, 645–671. (d) Yamaguchi, J.; Itami, K. Biaryl synthesis through metal-catalyzed C–H arylation. In *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijre, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2014; Vol 3, Chapter 17, pp 1315–1387. (e) Djakovitch, L.; Felpin, F.-X. *ChemCatChem* **2014**, 6, 2175–2178. (f) Shibahara, F.; Murai, T. *Asian J. Org. Chem.* **2013**, 2, 624–636. (g) Daugulis, O. *Chem. Heterocycl. Compd.* **2012**, 48, 21–26. (h) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, 51, 10236–10254. (i) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, 45, 788–802. (j) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, 112, 5879–5918. (k) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Tetrahedron* **2012**, 68, 5130–5136. (l) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, 40, 1992–2002. (m) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, 40, 1976–1991. (n) Schnurch, M.; Dastbaravardeh, N.; Ghobrial, M.; Mrozek, B.; Mihovilovic, M. D. *Curr. Org. Chem.* **2011**, 15, 2694–2730. (o) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Della Ca', N.; Maestri, G. *Coord. Chem. Rev.* **2010**, 254, 456–469. (p) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, 65, 10269–10310. (q) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, 40, 35–41.

(5) (a) Eicher, T.; Hauptmann, S. *Five-Membered Heterocycles. In The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, 2nd ed.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2003; pp 52–79. (b) Katritzky, A. R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, 111, 7–15.

(6) (a) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, 9, 1449–1451. (b) Roy, D.; Mom, S.; Royer, S.; Lucas, D.; Hierso, J.-C.; Doucet, H. *ACS Catal.* **2012**, 2, 1033–1041.

(7) For some selected papers on the transition-metal-catalyzed direct C–H bond arylation of furans and (benzo)thiophenes with aryl chlorides, please see: (a) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, 9, 1449–1451. (b) Roy, D.; Mom, S.; Beaupérin, M.; Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2010**, 49, 6650–6654. (c) Ozdemir, I.; Gök, Y.; Özeroğlu, Ö.; Kaloğlu, M.; Doucet, H.; Bruneau, C. *Eur. J. Inorg. Chem.* **2010**, 2010, 1798–1805. (d) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, 75, 6998–7001. (e) Mom, S.; Beaupérin, M.; Roy, D.; Royer, S.; Amardeil, R.; Cattey, H.; Doucet, H.; Hierso, J.-C. *Inorg. Chem.* **2011**, 50, 11592–11603. (f) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, 76, 471–483. (g) Ghosh, D.; Lee, H. M. *Org. Lett.* **2012**, 14, 5534–5537. (h) Akkoç, S.; Gök, Y.; Akkurt, M.; Tahir, M. N. *Inorg. Chim. Acta* **2014**, 413, 221–230. (i) Mariconda, A.; Grisi, F.; Costabile, C.; Falcone, S.; Bertolasi, V.; Longo, P. *New J. Chem.* **2014**, 38, 762–769.

(8) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, 31, 1951–1958.

(9) Biajoli, A. F. P.; da Penha, E. T.; Correia, C. R. D. *RSC Adv.* **2012**, 2, 11930–11935.

(10) (a) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, 9, 3137–3139. (b) Pereira, K.; Porter, A. L.; Potavathi, S.; LeBris, A. P.; DeBoef, B. *Tetrahedron* **2013**, 69, 4429–4435.

(11) Dao-Huy, T.; Haider, M.; Glatz, F.; Schnürch, M.; Mihovilovic, M. D. *Eur. J. Org. Chem.* **2014**, 2014, 8119–8125.

(12) (a) Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, 49, 1045–1048. (b) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, 130, 15185–15192. (c) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, 74, 1826–1834. (d) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, 75, 6998–7001. (e) Guchhait, S. K.; Kashyap, M.; Saraf, S. *Synthesis* **2010**, 2010, 1166–

1170. (f) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Chem. Sci.* **2012**, 3, 2165–2169. (g) Loukotova, L.; Yuan, K.; Doucet, H. *ChemCatChem* **2014**, 6, 1303–1309. (h) Pei, K.; Jie, X.-M.; Zhao, H.-Q.; Su, W.-P. *Eur. J. Org. Chem.* **2014**, 2014, 4230–4233.

(13) (a) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, 133, 4243–4245. (b) Truong, T.; Mesgar, M.; Le, K. K. A.; Daugulis, O. *J. Am. Chem. Soc.* **2014**, 136, 8568–8576.

(14) (a) Xiao, Z.-K.; Yin, H.-Y.; Lu, J.-M. *Inorg. Chim. Acta* **2014**, 423, 106–108. (b) Lv, H.; Zhu, L.; Tang, Y.-Q.; Lu, J.-M. *Appl. Organomet. Chem.* **2014**, 28, 27–31. (c) Yin, H.-Y.; Liu, M.-Y.; Shao, L.-X. *Org. Lett.* **2013**, 15, 6042–6045. (d) Xiao, Z.-K.; Yin, H.-Y.; Shao, L.-X. *Org. Lett.* **2013**, 15, 1254–1257. (e) Chen, W.-X.; Shao, L.-X. *J. Org. Chem.* **2012**, 77, 9236–9239. (f) Gao, T.-T.; Jin, A.-P.; Shao, L.-X. *Beilstein J. Org. Chem.* **2012**, 8, 1916–1919. (g) Zhu, L.; Ye, Y.-M.; Shao, L.-X. *Tetrahedron* **2012**, 68, 2414–2420. (h) Xiao, Z.-K.; Shao, L.-X. *Synthesis* **2012**, 44, 711–716. (i) Gu, Z.-S.; Shao, L.-X.; Lu, J.-M. *J. Organomet. Chem.* **2012**, 700, 132–134. (j) Zhu, L.; Gao, T.-T.; Shao, L.-X. *Tetrahedron* **2011**, 67, 5150–5155. (k) Tang, Y.-Q.; Lu, J.-M.; Shao, L.-X. *J. Organomet. Chem.* **2011**, 696, 3741–3744. (l) Zhou, X.-X.; Shao, L.-X. *Synthesis* **2011**, 2011, 3138–3142.

(15) (a) Shen, X.-B.; Zhang, Y.; Chen, W.-X.; Xiao, Z.-K.; Hu, T.-T.; Shao, L.-X. *Org. Lett.* **2014**, 16, 1984–1987. (b) Gu, Z.-S.; Chen, W.-X.; Shao, L.-X. *J. Org. Chem.* **2014**, 79, 5806–5811. (c) Ji, Y.-Y.; Lu, L.-L.; Shi, Y.-C.; Shao, L.-X. *Org. Biomol. Chem.* **2014**, 12, 8488–8498.

(16) Two other well-known and also easily available NHC-Pd(II) complexes from Nolan and Organ's groups with high catalytic activity in cross-coupling reactions were also checked for such reaction, and similar good results were achieved, respectively (see [Supporting Information](#) for more details). For selected papers, please see: (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, 4, 4053–4056. (b) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, 23, 1629–1635. (c) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. - Eur. J.* **2006**, 12, 4743–4748. (d) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, 48, 2383–2387.

(17) The additives maybe act as Lewis or Brønsted acids to activate benzo[b]furans in such transformation. For some selected examples, please see: (a) Tang, D.-T. D.; Collins, K. D.; Glorius, F. *J. Am. Chem. Soc.* **2013**, 135, 7450–7453. (b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, 131, 3291–3306. (c) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, 45, 7781–7786.

(18) Zhang, Y.; Xin, Z.-J.; Xue, J.-J.; Li, Y. *Chin. J. Chem.* **2008**, 26, 1461–1464.

(19) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, 11, 3954–3957.

(20) Duan, X.-F.; Zeng, J.; Zhang, Z.-B.; Zi, G.-F. *J. Org. Chem.* **2007**, 72, 10283–10286.

(21) Chen, C.-Y.; Dormer, P. G. *J. Org. Chem.* **2005**, 70, 6964–6967.

(22) Ge, S.-Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, 51, 12837–12841.

(23) Mongin, F.; Bucher, A.; Bazureau, J. P.; Bayh, O.; Awad, H.; Trécourt, F. *Tetrahedron Lett.* **2005**, 46, 7989–7992.

(24) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, 2007, 1491–1509.