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N-heterocyclic carbene–palladium(II)-1-methylimidazole complex-catalyzed Suzuki–Miyaura coupling of benzyl sulfonates with arylboronic acids†

Xiao-Xia Wang, Bin-Bin Xu, Wen-Ting Song, Kai-Xin Sun and Jian-Mei Lu*

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The first example of palladium-catalyzed Suzuki–Miyaura coupling between benzyl sulfonates and arylboronic acids was reported in this paper. In the presence of a well-defined, air-stable and easily available NHC–Pd(II)–Im complex, all reactions worked well to give the desired products in good to almost quantitative yields under the optimal conditions. Electron-rich, -neutral, -poor and sterically-hindered substituents on both substrates are tolerated in such transformation, providing a convenient, efficient and alternative method for the synthesis of diarylmethanes.

Introduction

Transition metal catalyzed Suzuki–Miyaura coupling reactions are among the most important reactions for the formation of carbon–carbon bonds.[1] In such transformations, aryl halides are usually used as the electrophiles. Disappointingly, some obvious drawbacks are involved with the use of aryl halides as they are not easily available and are not environmentally friendly both in themselves and the halides-containing by-products. During recent years, O-based alternative electrophiles have attracted much attention because they are more easily available from phenol derivatives or carbonyl enolates and they are also sometimes cheaper.[2] In addition, the use of O-based electrophiles instead of their halide counterparts will avoid the toxic halide-containing by-products. However, compared to the abundant papers on transition metal catalyzed coupling reactions of O-based electrophiles derived from phenols with aryl organoborons, similar electrophiles derived from benzyl alcohols are rarely reported,[3] suggesting great potential in this field.

Recently, Shao and our group have successfully developed a well-defined N-heterocyclic carbene–Pd(II)-1-methylimidazole [NHC–Pd(II)–Im] complex **1**,[4] and found it to be an efficient catalyst for the Suzuki–Miyaura coupling of benzyl chlorides and aryl tosylates with aryl organoborons.[5] Considering our successful experience with the applications of this complex in these two reactions, we then turned our recent interest to the coupling reaction between benzyl sulfonates and arylboronic acids for the formation of diarylmethanes,[6] which are important subunits in molecules with pharmaceutical activities[7] and supramolecules.[8] Herein, we report the first example of Pd-catalyzed coupling reactions of benzyl sulfonates with arylboronic acids in detail.

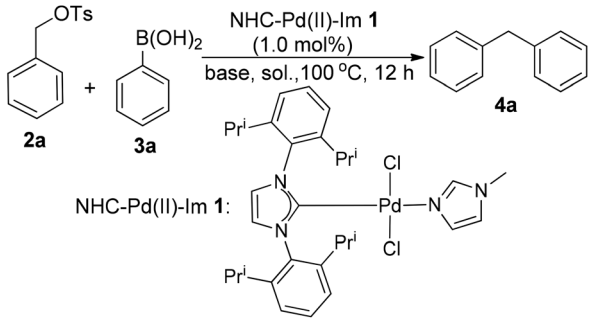
Results and discussion

The reaction between benzyl tosylate **2a** (1.2 equiv.) and phenylboronic acid **3a** (0.70 mmol) in the presence of NHC–Pd(II)–Im complex **1** (1.0 mol%) was chosen as the first model reaction to test the effects of bases and solvents. The results are summarized in Table 1. For instance, in the first round, the reaction was performed in THF (2.0 mL) at 100 °C for 12 h to evaluate various bases (Table 1, entries 1–8). Of the bases screened, $K_3PO_4{\cdot}3H_2O$ and NaOH showed the best yields (Table 1, entries 2 and 4). Product **4a** can also be obtained in good yields when KOH and Cs_2CO_3 were used, respectively (Table 1, entries 6 and 7). In the presence of other bases such as K_2CO_3, $NaHCO_3$, Na_2CO_3 and $KHCO_3$, very low yields were observed (Table 1, entries 1, 3, 5 and 8). Considering the lower molecular weight and lower cost, NaOH was chosen as the best base for further optimization. Further study showed that 100 °C was necessary for such transformations.[9] For example, when the model reaction was performed in THF at 90 °C for 12 h, product **4a** was obtained in lower yield (80%). Using NaOH as the base, a variety of solvents was also examined, giving inferior yields in most cases. For example, when other solvents such as CH_3CN and toluene were used, very low yields

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang Province 325035, People's Republic of China. E-mail: ljm@wzu.edu.cn; Fax: +86 57786689300; Tel: +86 57786689300

† Electronic supplementary information (ESI) available: Copy of ^1H and ^{13}C NMR spectra of compounds **4**. See DOI: 10.1039/c4ob02675f

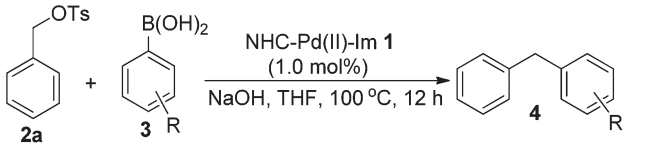
Table 1 Optimization for complex **1** catalyzed reaction between benzyl tosylate **2a** and phenylboronic acid **3a**



Entry[a]	Base	Solvent	Yield[b] (%)
1	K_2CO_3	THF	26
2	$K_3PO{\cdot}3H_2O$	THF	96
3	$NaHCO_3$	THF	7
4	NaOH	THF	93
5	Na_2CO_3	THF	25
6	KOH	THF	80
7	Cs_2CO_3	THF	88
8	$KHCO_3$	THF	11
9	NaOH	Morpholine	<5
10	NaOH	CH_3CN	29
11	NaOH	DMF	6
12	NaOH	Toluene	60
13	NaOH	DMSO	NR
14	NaOH	Dioxane	90

[a] All reactions were carried out using **2a** (0.84 mmol), **3a** (0.7 mmol), base (1.5 equiv.), **1** (1.0 mol%) in solvent (2.0 mL) at 100 °C for 12 h. [b] Isolated yields.

Table 2 NHC–Pd(II)–Im complex **1**-catalyzed reactions between benzyl tosylate **2a** and arylboronic acids **3**



Entry[a]	**3** (R)	Yield[b] (%)
1	**3b** (4-OMe)	**4b**, 92
2	**3c** (3-OMe)	**4c**, 96
3	**3d** (2-OMe)	**4d**, 97
4	**3e** (4-Me)	**4e**, 89
5	**3f** (2-Me)	**4f**, 94
6	**3g** (2,6-Me_2)	**4g**, 88
7	**3h** (3,5-Me_2)	**4h**, 96
8	**3i** (4-Ph)	**4i**, 91
9	**3j** (4-vinyl)	**4j**, 81
10	**3k** (4-F)	**4k**, 83
11	**3l** (4-CO_2Et)	**4l**, 88
12	**3m** (4-CF_3)	**4m**, 82
13	**3n** (1-naphthalenyl)	**4n**, 99

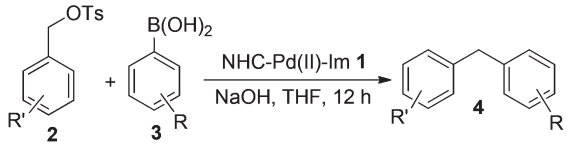
[a] All reactions were carried out using **2a** (0.84 mmol), **3** (0.7 mmol), NaOH (1.5 equiv.), **1** (1.0 mol%) in THF (2.0 mL) at 100 °C for 12 h. [b] Isolated yields.

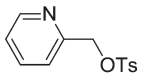
were observed (Table 1, entries 10 and 12). In addition, when using morpholine, DMF and DMSO as the solvent, respectively, almost no desired product can be formed (Table 1, entries 9, 11 and 13). It is noteworthy that in Shao's previous papers, it was found that morpholine was the best solvent for the Suzuki–Miyaura coupling of aryl sulfonates and sulfamates with arylboronic acids, perhaps due to the formation of NHC–Pd(II)–morpholine complex as the real precatalyst.[5b,10] However, in the current reaction between benzyl tosylate **2a** and phenylboronic acid **3a**, morpholine was not a suitable solvent, suggesting that the NHC–Pd(II)–morpholine complex was not the active precatalyst in the current transformation. Using dioxane as the solvent, a comparable yield was obtained (Table 1, entry 14).

With the optimal reaction conditions established, the reactions between phenyl tosylate **2a** and various arylboronic acids **3** were then investigated (Table 2). As can be seen from Table 2, all reactions proceeded smoothly to give the desired coupling products **4** in good to almost quantitative yields. It seemed that substituents on the arylboronic acids **3** almost had no effect on the reactions. For example, electron-rich substituents such as MeO and Me or electron-poor substituents such as F atom and even strongly electron-withdrawing groups such as CO_2Et and CF_3 were all tolerated, giving products **4** in good to very high yields. In addition, sterically-hindered substituents on the arylboronic acids **3** were also tolerated in this transformation. For instance, for the reactions involving 2-methoxyphenylboronic acid **3d**, 2-methylphenylboronic acid **3f** and 2,6-dimethylphenylboronic acid **3g**, good to high yields were obtained (Table 2, entries 3, 5 and 6). The same substituent on a different position of the phenyl groups of arylboronic acids **3** also did not affect the reactions. For example, comparable yields can be obtained when arylboronic acids **3**, having a methoxy group on the 2-, 3- or 4-position on the phenyl ring, were used as the substrates (Table 2, entries 1–3).

The scope of this reaction was further tested using different benzyl tosylates **2** and arylboronic acids **3** under the optimized conditions. The results are summarized in Table 3. All reactions took place to give the desired products **4** in good to almost quantitative yields. Electron-rich, -neutral, -poor and sterically-hindered substituents on both substrates were tolerated. For instance, reactions involving sterically-hindered substituted substrates such as 2-methylbenzyl tosylate **2d**, 2-methylphenylboronic acid **3f** and 2-methoxyphenylboronic acid **3d** proceeded well to give the corresponding coupling products **4** in good to almost quantitative yields (Table 3, entries 3, 7, 12–14, 16 and 19). Benzyl tosylate **2f**, having a strongly electron-withdrawing group such as nitro group on the phenyl ring, was also a suitable substrate to give product **4p** in high yield (Table 3, entry 5). Substrate **2g** having heteroaryl ring substituent was also suitable for such transformation to afford products **4ab** and **4ac** in good yields under appropriate conditions (Table 3, entries 18 and 19).

Table 3 NHC–Pd(II)–Im complex **1**-catalyzed reactions between benzyl tosylates **2** and arylboronic acids **3**

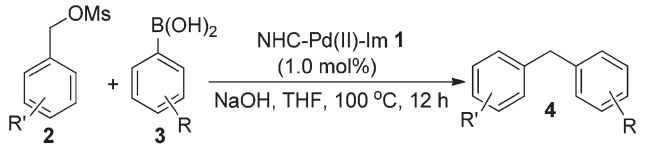


Entry[a]	2 (R′)	3 (R)	Yield[b] (%)
1	**2b** (3-OMe)	**3a** (H)	**4c**, 96
2	**2c** (3-Me)	**3a**	**4o**, 99
3	**2d** (2-Me)	**3a**	**4f**, 94
4	**2e** (4-F)	**3a**	**4k**, 99
5	**2f** (4-NO_2)	**3a**	**4p**, 94
6	**2b**	**3b** (4-OMe)	**4q**, 99
7	**2b**	**3f** (2-Me)	**4r**, 93
8	**2b**	**3k** (4-F)	**4s**, 99
9	**2c**	**3b**	**4t**, 99
10	**2c**	**3i** (4-Ph)	**4u**, 94
11	**2c**	**3c** (3-OMe)	**4v**, 97
12	**2d**	**3b**	**4w**, 99
13	**2d**	**3i**	**4x**, 93
14	**2d**	**3c**	**4r**, 88
15	**2e**	**3b**	**4y**, 96
16	**2e**	**3f**	**4z**, 99
17	**2e**	**3k**	**4aa**, 82
18[c]	**2g** 	**3b**	**4ab**, 83
19[c]		**3d** (2-OMe)	**4ac**, 82

[a] If not otherwise specified, all reactions were carried out using **2** (0.84 mmol), **3** (0.7 mmol), NaOH (1.5 equiv.), **1** (1.0 mol%) in THF (2.0 mL) at 100 °C for 12 h. [b] Isolated yields. [c] Reaction conditions: **1** (2.0 mol%), 140 °C.

Besides tosylates, it seems that mesylates are more attractive because they are more atom economical substrates than tosylates due to their lower molecular weight. However, mesylates are more inert than tosylates due to the higher stability of the C–O bonds in such materials,[11] resulting in difficulties in C–O bond activation/cleavage in the oxidative step in the metal-catalyzed coupling reactions, implying that mesylates are more challenging substrates in coupling reactions. Therefore, based on the above successful results in the NHC–Pd(II)–Im complex **1** catalyzed Suzuki–Miyaura coupling between benzyl tosylates and arylboronic acids, we then turned our interest to such transformations using the more challenging benzyl mesylates as the substrates. To our pleasure, the optimal reaction conditions are also suitable for benzyl mesylates. For instance, as can be seen from Table 4, all reactions worked well to afford the desired products **4** in good to almost quantitative yields under identical conditions. Electron-rich, -neutral, -poor and sterically-hindered substituents on both substrates were also tolerated. For example, all reactions of benzyl mesylate **2g** with phenylboronic acid **3a**, 4-methoxyphenylboronic acid **3b**, 2-methylphenylboronic acid **3f** and 4-fluorophenylboronic acid **3k** worked well enough to give products **4** in good to almost quantitative yields (Table 4, entries 1–4).

Table 4 NHC–Pd(II)–Im complex **1**-catalyzed reactions between benzyl mesylates **2** and arylboronic acids **3**



Entry[a]	2 (R′)	3 (R)	Yield[b] (%)
1	**2g** (H)	**3a** (H)	**4a**, 99
2	**2g**	**3b** (4-OMe)	**4b**, 99
3	**2g**	**3f** (2-Me)	**4f**, 86
4	**2g**	**3k** (4-F)	**4k**, 85
5	**2h** (4-OMe)	**3a**	**4b**, 98
6	**2h**	**3b**	**4ad**, 97
7	**2h**	**3f**	**4w**, 99
8	**2h**	**3i** (4-Ph)	**4ae**, 92
9	**2i** (4-F)	**3a**	**4k**, 88
10	**2i**	**3b**	**4y**, 93
11	**2i**	**3f**	**4z**, 90
12	**2i**	**3i**	**4af**, 90

[a] All reactions were carried out using **2** (0.84 mmol), **3** (0.7 mmol), NaOH (1.5 equiv.), **1** (1.0 mol%) in THF (2.0 mL) at 100 °C for 12 h. [b] Isolated yields.

Conclusions

In conclusion, the first example of a palladium-catalyzed Suzuki–Miyaura coupling between benzyl sulfonates and arylboronic acids is reported in this paper. Under the optimal conditions, various aryl tosylates and mesylates reacted with arylboronic acids very well to give the desired coupling products in good to almost quantitative yields. The scope and limitations of this transformation was fully discussed in this paper, and it was found that electron-rich, -neutral, -poor and sterically-hindered substituents on both substrates can be tolerated in such transformation, thus providing a convenient, efficient and alternative method for the synthesis of diarylmethanes.

Experimental

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 used for high resolution mass spectra (HRMS, EI) is FT-ICR. 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 reactions between benzyl sulfonates 2 and arylboronic acids 3

Under N_2 atmosphere, benzyl sulfonates **2** (0.84 mmol), arylboronic acids **3** (0.7 mmol), NHC–Pd(II)–Im complex **1**

(1.0 mol%), NaOH (1.5 equiv.) and THF (2.0 mL) were successively added to a sealed tube. The mixture was stirred vigorously at 100 °C for 12 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (petroleum ether as the eluent) to give the pure products **4**.

Compound 4a.[5a] Colorless liquid (109.5 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.28–7.25 (m, 4H), 7.19–7.17 (m, 6H), 3.97 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 128.9, 128.4, 126.0, 41.9.

Compound 4b.[5a] Yellow liquid (127.5 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.257 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 3H), 7.08 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 3.90 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 141.5, 133.2, 129.8, 128.8, 128.4, 125.9, 113.9, 55.1, 41.0.

Compound 4c.[12] Yellow liquid (133.1 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ, 7.26 (t, J = 7.5 Hz, 2H), 7.20–7.17 (m, 4H), 6.77 (d, J = 7.5 Hz, 1H), 6.74–6.72 (m, 2H), 3.94 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 142.7, 140.9, 129.4, 128.9, 128.4, 126.0, 121.3, 114.8, 111.3, 55.0, 41.9.

Compound 4d.[5a] Yellow liquid (134.4 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.25 (t, J = 7.5 Hz, 2H), 7.20–7.14 (m, 4H), 7.05 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 3.97 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 141.0, 130.3, 129.6, 128.9, 128.2, 127.4, 125.7, 120.4, 110.4, 55.3, 35.8.

Compound 4e.[5a] Colorless liquid (113.4 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.26 (t, J = 7.5 Hz, 2H), 7.19–7.165 (m, 3H), 7.08 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 3.93 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 138.0, 135.4, 129.1, 128.83, 128.78, 128.4, 125.9, 41.5, 21.0.

Compound 4f.[12] Colorless liquid (119.7 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.26 (t, J = 7.5 Hz, 2H), 7.19–7.08 (m, 7H), 3.98 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 138.9, 136.6, 130.3, 129.9, 128.7, 128.4, 126.4, 126.0, 125.9, 39.4, 19.6.

Compound 4g.[13] Colorless liquid (120.7 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS δ 7.20 (d, J = 7.5 Hz, 2H), 7.16–7.12 (m, 1H), 7.10–7.04 (m, 3H), 7.00 (d, J = 7.5 Hz, 2H), 4.05 (s, 2H), 2.23 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 137.1, 136.8, 128.3, 128.1, 127.8, 126.3, 125.7, 35.0, 20.2.

Compound 4h.[5a] Colorless liquid (131.7 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.26 (t, J = 7.5 Hz, 2H), 7.19–7.16 (m, 3H), 6.82 (s, 1H), 6.80 (s, 2H), 3.89 (s, 2H), 2.26 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 140.9, 137.9, 128.9, 128.4, 127.7, 126.8, 125.9, 41.8, 21.2.

Compound 4i.[5a] White solid (155.4 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.56 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.32–7.19 (m, 8H), 4.01 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 140.2, 139.0, 129.3, 128.9, 128.7, 128.5, 127.2, 127.1, 127.0, 126.1, 41.6.

Compound 4j.[12] Colorless liquid (110.0 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.33 (d, J = 7.0 Hz, 2H), 7.28 (t, J = 7.0 Hz, 2H), 7.21–7.14 (m, 5H), 6.68 (dd, J = 17.5, 11.0 Hz, 1H), 5.70 (dd, J = 17.5, 1.0 Hz, 1H), 5.19 (dd, J = 11.0, 1.0 Hz, 1H), 3.96 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 140.8, 136.6, 135.5, 129.1, 128.9, 128.5, 126.3, 126.1, 113.2, 41.6.

Compound 4k.[5a] Yellow liquid (108.0 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.29 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.19–7.12 (m, 4H), 6.96 (t, J = 8.5 Hz, 2H), 3.95 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.41 (d, J_{C-F} = 242.5 Hz), 140.9, 136.7 (d, J_{C-F} = 3.25 Hz), 130.2 (d, J_{C-F} = 7.875 Hz), 128.8, 128.5, 126.2, 115.2 (d, J_{C-F} = 21.0 Hz), 41.0.

Compound 4l.[14] Yellow liquid (147.8 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.96 (d, J = 8.5 Hz, 2H), 7.29–9.19 (m, 5H), 7.16 (d, J = 7.5 Hz, 2H), 4.35 (q, J = 7.0 Hz, 2H), 4.01 (s, 2H), 1.36 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 146.3, 140.1, 129.7, 128.9, 128.8, 128.5, 128.4, 126.3, 60.7, 41.8, 14.3.

Compound 4m.[15] Colorless liquid (135.5 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.52 (d, J = 8.0 Hz, 2H), 7.31–7.27 (m, 4H), 7.23–7.20 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 4.02 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 140.0, 129.2, 128.9, 128.5 (q, J_{C-F} = 32.125 Hz), 127.6, 126.5, 125.39 (q, J_{C-F} = 3.75 Hz), 124.3 (q, J_{C-F} = 270.125 Hz), 41.7.

Compound 4n.[5a] Colorless liquid (151.1 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.78–7.72 (m, 3H), 7.61 (s, 1H), 7.44–7.38 (m, 2H), 7.30–7.26 (m, 3H), 7.22–7.16 (m, 3H), 4.12 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 138.5, 133.6, 132.1, 129.0, 128.4, 128.0, 127.6, 127.5, 127.1, 126.1, 125.9, 125.3, 42.0.

Compound 4o.[5a] Colorless liquid (126.1 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.27 (t, J = 7.5 Hz, 2H), 7.18–7.15 (m, 4H), 7.00–6.97 (m, 3H), 3.93 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 141.0, 138.0, 129.7, 128.9, 128.4, 128.3, 126.8, 125.99, 125.96, 41.9, 21.4.

Compound 4p.[16] Yellow liquid (140.2 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.13 (d, J = 9.0 Hz, 2H), 7.34–7.30 (m, 4H), 7.26–7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 4.07 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 146.5, 139.2, 129.6, 128.9, 128.8, 126.7, 123.7, 41.7.

Compound 4q. Yellow liquid (158.0 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.18 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.77–6.71 (m, 3H), 3.88 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 158.0, 143.1, 133.0, 129.8, 129.3, 121.2, 114.6, 113.8, 111.2, 55.1, 55.0, 41.0. MS (EI, %) m/z 212 (M^+, 100), 197 (57), 121 (28). HRMS (EI) calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1147. IR (neat) ν 2935, 2829, 1606, 1583, 1483, 1436, 1298, 1245, 1172, 1149, 1036, 830, 819, 783, 753, 741, 690 cm^{-1}.

Compound 4r. Yellow liquid (138.0 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.19–7.09 (m, 5H), 6.72 (t, J = 6.5 Hz, 2H), 6.67 (s, 1H), 3.95 (s, 2H), 3.74 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 142.1, 138.7, 136.6, 130.2, 129.9, 129.3, 126.4, 126.0, 121.2, 114.7, 111.1, 55.1, 39.4, 19.6. MS (EI, %) m/z 212 (M^+, 100), 197 (43), 104 (42). HRMS (EI) calcd for $C_{15}H_{16}O$: 212.1201, found: 212.1202. IR (neat) ν 2934, 2828, 1596, 1487, 1454, 1315, 1255, 1139, 1053, 765, 735, 690 cm^{-1}.

Compound 4s. Yellow liquid (149.7 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.19 (t, J = 7.5 Hz, 1H), 7.12 (dd, J =

8.5, 5.5 Hz, 2H), 6.94 (t, J = 8.5 Hz, 2H), 6.75–6.73 (m, 2H), 6.70 (s, 1H), 3.90 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, J_{C-F} = 242.375 Hz), 159.8, 142.5, 136.6 (d, J_{C-F} = 3.125 Hz), 130.2 (d, J_{C-F} = 7.75 Hz), 129.4, 121.2, 115.1 (d, J_{C-F} = 21.125 Hz), 114.7, 111.3, 55.0, 41.0. MS (EI, %) m/z 216 (M^+, 100). HRMS (EI) calcd for $C_{14}H_{13}FO$: 216.0950, found: 216.0945. IR (neat) ν 2941, 2829, 1597, 1580, 1487, 1454, 1434, 1252, 1219, 1156, 1050, 821, 781, 741, 690 cm^{-1}.

Compound 4t.[17] Yellow liquid (147.0 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.16 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.00–6.96 (m, 3H), 6.82 (d, J = 8.0 Hz, 2H), 3.88 (s, 2H), 3.77 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 141.5, 138.0, 133.4, 129.8, 129.6, 128.3, 126.7, 125.8, 113.9, 55.2, 41.0, 21.4.

Compound 4u. Colorless liquid (169.8 mg, 94%). Mp: 60–62 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.54 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.02–7.00 (m, 3H), 3.95 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 140.9, 140.4, 139.0, 138.0, 129.7, 129.3, 128.7, 128.4, 127.1, 127.02, 126.96, 126.9, 126.0, 41.5, 21.4. MS (EI, %) m/z 258 (M^+, 100), 243 (45), 165 (38). HRMS (EI) calcd for $C_{20}H_{18}$: 258.1409, found: 258.1407. IR (neat) ν 1606, 1484, 1411, 1335, 1003, 915, 882, 848, 818, 785, 765, 740, 688 cm^{-1}.

Compound 4v. Yellow liquid (143.9 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.19–7.12 (m, 2H), 7.05–6.97 (m, 4H), 6.87–6.83 (m, 2H), 3.93 (s, 2H), 3.78 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 140.9, 137.7, 130.3, 129.8, 129.7, 128.1, 127.3, 126.5, 126.0, 120.4, 110.4, 55.3, 35.7, 21.4. MS (EI, %) m/z 212 (M^+, 100), 197 (53), 181 (38), 165 (39). HRMS (EI) calcd for $C_{15}H_{16}O$: 212.1201, found: 212.1199. IR (neat) ν 3021, 2921, 2835, 1600, 1494, 1457, 1249, 1186, 1106, 1050, 1033, 798, 750, 695 cm^{-1}.

Compound 4w.[17] Yellow liquid (146.9 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.13–7.11 (m, 3H), 7.07–7.06 (m, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 3.90 (s, 2H), 3.74 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 139.3, 136.4, 132.4, 130.2, 129.7, 129.6, 126.3, 125.9, 113.8, 55.1, 38.5, 19.5.

Compound 4x. White solid (168.0 mg, 93%). Mp: 72–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.54 (d, J = 7.5 Hz, 2H), 7.48 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.18–7.14 (m, 6H), 4.00 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 139.5, 138.9, 138.8, 136.6, 130.3, 129.9, 129.1, 128.7, 127.1, 127.0, 126.9, 126.5, 126.0, 39.1, 19.7. MS (EI, %) m/z 258 (M^+, 100), 243 (49), 165 (36), 104 (37). HRMS (EI) calcd for $C_{20}H_{18}$: 258.1409, found: 258.1413. IR (neat) ν 2954, 1597, 1507, 1481, 1441, 1401, 1378, 1109, 1070, 1003, 904, 814, 771, 756, 746, 725, 695 cm^{-1}.

Compound 4y.[17] Yellow liquid (145.2 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.10 (dd, J = 8.5, 5.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 6.94 (t, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.87 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, J_{C-F} = 242.25 Hz), 158.1, 137.2 (d, J_{C-F} = 3.25 Hz), 133.0, 130.1 (d, J_{C-F} = 7.75 Hz), 129.7, 115.1 (d, J_{C-F} = 21.0 Hz), 113.9, 55.2, 40.2.

Compound 4z. Colorless liquid (138.6 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.16–7.13 (m, 3H), 7.07–7.04 (m, 3H), 6.94 (t, J = 8.5 Hz, 2H), 3.93 (s, 2H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (d, J_{C-F} = 242.25 Hz), 138.7, 136.5, 136.0 (d, J_{C-F} = 3.125 Hz), 130.4, 130.0 (d, J = 7.75 Hz), 129.8, 126.6, 126.1, 115.1 (d, J_{C-F} = 21.0 Hz), 38.6, 19.6. MS (EI, %) m/z 200 (96), 185 (M^+, 100), 165 (29). HRMS (EI) calcd for $C_{14}H_{13}F$: 200.1001, found: 200.1002. IR (neat) ν 3018, 2917, 1606, 1511, 1228, 1157, 1092, 842, 819, 778, 737 cm^{-1}.

Compound 4aa. Colorless liquid (117.1 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.11 (dd, J = 8.5, 5.5 Hz, 2H), 6.97 (t, J = 8.5 Hz, 4H), 3.92 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (d, J_{C-F} = 242.75 Hz), 136.6 (d, J_{C-F} = 3.125 Hz), 130.2 (d, J_{C-F} = 7.75 Hz), 115.3 (d, J_{C-F} = 21.125 Hz), 40.2. MS (EI, %) m/z 204 (M^+, 100), 183 (47). HRMS (EI) calcd for $C_{13}H_{10}F_2$: 204.0751, found: 204.0749. IR (neat) ν 3034, 2927, 1603, 1507, 1225, 1156, 1099, 1010, 851, 819, 763 cm^{-1}.

Compound 4ab.[17] Yellow liquid (115.6 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.52 (d, J = 4.0 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 2H), 7.08–7.06 (m, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.09 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 158.1, 149.1, 136.3, 131.5, 129.9, 122.8, 121.0, 113.9, 55.1, 43.7.

Compound 4ac.[18] Yellow liquid (114.2 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.52 (d, J = 4.5 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 HZ, 1H), 7.09–7.05 (m, 2H), 6.92–6.86 (m, 2H), 4.17 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.4, 149.0, 136.2, 130.8, 127.9, 127.7, 122.9, 120.8, 120.6, 110.5, 55.3, 38.7.

Compound 4ad.[19] White solid (154.8 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.07 (d, J = 9.0 Hz, 4H), 6.80 (d, J = 9.0 Hz, 4H), 3.84 (s, 2H), 3.74 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 133.7, 129.7, 113.8, 55.2, 40.1.

Compound 4ae. White solid (176.4 mg, 92%). Mp: 86–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.55 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.93 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 141.0, 140.7, 138.9, 133.1, 129.8, 129.2, 128.7, 127.1, 127.0, 126.9, 113.9, 55.2, 40.6. MS (EI, %) m/z 274 (M^+, 100). HRMS (EI) calcd for $C_{20}H_{18}O$: 274.1358, found: 274.1354. IR (neat) ν 3023, 2946, 2923, 2828, 1612, 1579, 1505, 1313, 1293, 1245, 1171, 1106, 1030, 908, 855, 817, 802, 766, 756, 728, 700 cm^{-1}.

Compound 4af. White solid (165.1 mg, 90%). Mp: 58–59 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.14 (dd, J = 8.0, 5.5 Hz, 2H), 6.96 (t, J = 8.0 Hz, 2H), 3.95 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (d, J_{C-F} = 242.625 Hz), 140.9, 140.0, 139.2, 136.6 (d, J_{C-F} = 3.125 Hz), 130.3 (d, J_{C-F} = 7.75 Hz), 129.2, 128.7, 127.2, 127.1, 127.0, 115.2 (d, J_{C-F} = 21.0 Hz), 40.7. MS (EI, %) m/z 262 (M^+, 100). HRMS (EI) calcd for $C_{19}H_{15}F$: 262.1158, found:

262.1157. IR (neat) ν 2917, 2846, 1600, 1505, 1488, 1437, 1402, 1216, 1157, 865, 824, 807, 775, 745, 728, 686 cm^{-1}.

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