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Article

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A copper catalyzed Formal [3+2]-Cycloaddition for the Synthesis of All Different Aryl-Substituted Furan and Thiophene

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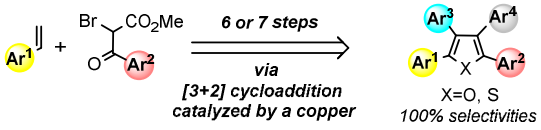
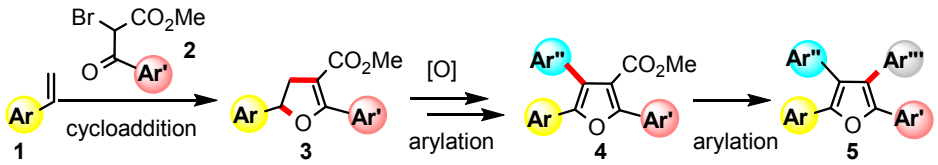


ABSTRACT: A highly efficient formal [3+2] cycloaddition was established using a copper catalyst. The resulting dihydrofurans were subjected to oxidation followed by arylations to produce tetraaryl furans. In addition, the dihydrofuran can be converted to diaryl dihydrothiophene by using Lawesson's reagent. This protocol will facilitate the synthesis of all different aryl-substituted furan and thiophene.

INTRODUCTION

Multiply substituted furans are valuable molecules because various bioactive compounds contain furan units[1,2]. Although numerous methods of synthesizing substituted furans have been developed[3,4], synthetic methods for accessing possible isomers of a furan are not currently well developed, because unlike thiophenes and other heteroaromatics[5], the regioselective substitution of a furan is very difficult. We herein report an efficient synthetic protocol for preparing various aryl-substituted furans **5** via the cycloaddition of styrene **1** followed by sequential arylations (Scheme 1).

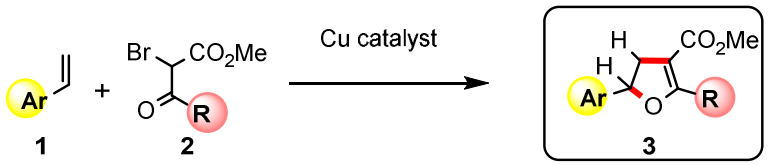
Scheme 1. The synthesis of various aryl-substituted furans 5



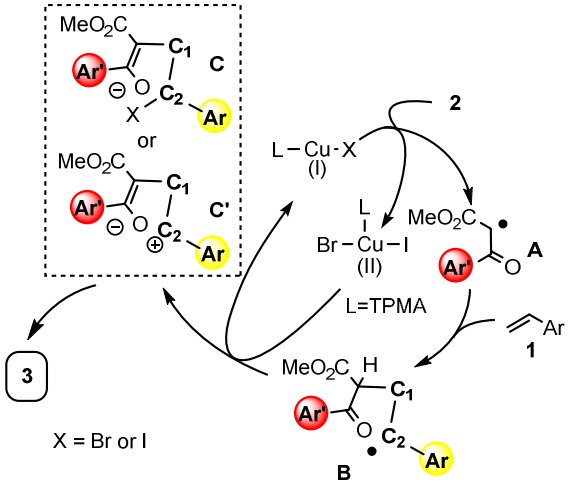
The goal of our current protocol is to successfully achieve a formal [3+2] cycloaddition of styrenes **1** and ketoesters **2** to produce dihydrofurans **3**[6]. Dihydrofurans or furan derivatives have been synthesized in the past by reacting 1,3-dicarbonyl compounds in the presence or absence of a large excess of metal salts[7,8]. Traditional methods such as the Paal–Knorr synthesis[9] are reliable for the synthesis of various furans and their related rings. In addition, radical reactions are one of the most convenient protocols for the synthesis of dihydrofurans

and furan derivatives. For example, Lei's group recently reported on a methodology that employs iodine as a catalyst for the synthesis of dihydrofurans and furans[8a,b]. Hajra's group also synthesized furans from β-nitrostyrenes or α,β–unsaturated carbonyl compounds[8c,d]. Flowers' group successively obtained substituted furans using Ce(IV)[8e]. Conversely, during the course of our research in atom transfer radical reactions[10], we discovered that a copper catalyst is extremely effective at promoting the formal [3+2] cycloaddition reaction of styrene and 2-bromoketoesters (Scheme 2). We hypothesize that this reaction undergoes a typical atom-transfer radical reaction via intermediate **A** (Scheme 3)[11]. Previous results demonstrated that the reaction starts with the generation of alkyl radical species **A** from the reaction between Cu(I) and **2**[10b]. After the generation of **A**, the addition of **A** to **1** gives radical intermediate **B**. Intermediate **B** can either react with a Cu(II) salt to produce intermediate **C** or be oxidized by the Cu(II) species to produce intermediate **C'** with the concomitant formation of a Cu(I) species to complete the catalytic cycle. The generation of **C** or **C'** is somewhat controversial in this radical chemistry. Intermediate **C** or **C'** undergoes intramolecular cyclization to give the desired product **3**.

Scheme 2. A formal [3+2] cycloaddition catalyzed by a copper salt.



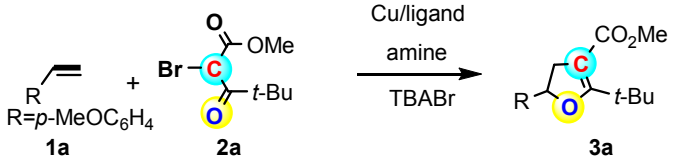
Scheme 3. Proposed mechanism.



RESULTS&DISCUSSION

In our initial experiments, 16% yield of dihydrofuran **3a** was obtained when bromoketoester **2a** was employed for the reaction (Table 1 entry 1). During the reaction, **1a** and **2a** were consumed due to the generation of the corresponding dehalogenated product and polymer. [Cu(Me_2S)]Br slightly increased the yield but other catalysts were not effective (entry 2). Addition of amine was crucial, and *i*-Pr_2NH gave **3a** in 36% yield. However, other amines, such as *t*-BuMeNH, CyMeNH, *t*-$BuNH_2$, Et_3N, *i*-Pr_2NEt, and pyridine, were not effective (entry 3). We also tested the effects of ligands, temperature, and ammonium salts but higher yields were not obtained (entries 4–6). Significant progress was obtained in the solvent screening. CH_2Cl_2 gave 33% yield at 60 °C; surprisingly, the yield increased to 87% at 80 °C (entry 7). In this case, all starting materials were consumed, and longer reaction time was not effective to obtain higher yield. Other solvents, such as toluene, xylene, and CH_2ClCH_2Cl, were not effective. The combination of tris(2-pyridylmethyl)amine (TPMA), Bu_4NNO_2(TBA-NO_2), CH_2Cl_2, and 80°C was crucial to obtain the highest yield. Contrary to our previous works[10], Cu(II) gave the best result among copper catalyst, such as CuI, CuBr, CuCl, and CuI·SMe_2. Generally, bromoesters **2** react with Cu(I) not Cu(II) to produce the corresponding alkyl radical species for the atom transfer radical addition or polymerization[12]. To undergo current [3+2] cycloaddition, Cu(II) must be reduced to Cu(I). But, in this reaction, any reductant, such as low-valent metals, Sn(II), glucose, hydrazine, and ascorbic acid, were not used to generate active Cu(I) species from Cu(II) species. Weiss and co-workers have reported that excess amine can reduce Cu(II) to Cu(I)[12]. Therefore, *i*-Pr_2NH could act as a reductant. The effect of Bu_4NNO_2 is not clear; however, it may be that the nitrite ion acts as a reducing agent to generate active Cu(I) species or it may increase the single electron transfer ability[12].

Table 1. Optimizations.

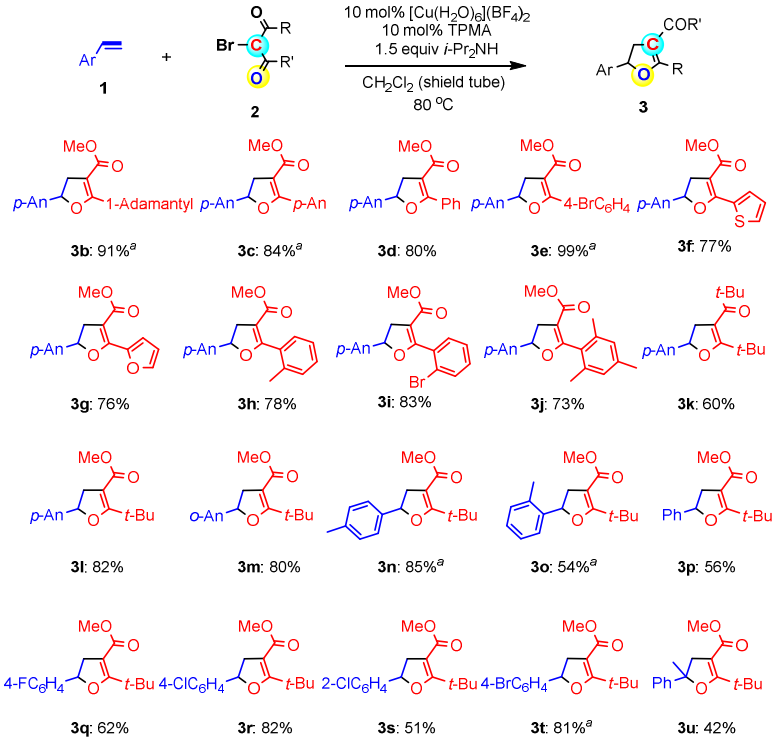


entry	Cu	ligand	amine	solvent	yield of **3a**(%)
1[a]	CuI	none	PMDETA	toluene	16
2[a]	[Cu(Me_2S)]Br	none	PMDETA	toluene	21
3[a]	[Cu(Me_2S)]Br	none	*i*-Pr_2NH	toluene	36
4[a]	[Cu(Me_2S)]Br	TPMA	*i*-Pr_2NH	toluene	35
5[a]	[Cu(H_2O)$_6$](BF_4)$_2$	TPMA	*i*-Pr_2NH	toluene	35
6[b,c]	[Cu(H_2O)$_6$](BF_4)$_2$	TPMA	*i*-Pr_2NH	toluene	33
7[b,c]	**[Cu(H_2O)$_6$](BF_4)$_2$**	**TPMA**	***i*-Pr_2NH**	**CH_2Cl_2**	**87**
8[a,c]	[Cu(H_2O)$_6$](BF_4)$_2$	TPMA	*i*-Pr_2NH	CH_2Cl_2	33

All reactions were carried out in shield tubes for 20 h in toluene or CH_2Cl_2 with 10 mol% Cu salt, amine (1.5 equiv.), ligand (0 or 10 mol%), Bu_4NBr(or -NO_2) (0 or 20 mol%), **1a** (1 equiv.) and **2a** (2.0 equiv.). Yields were determined by ^{1}HNMR. [a] Run at 60°C. [b] Run at 80°C. [c] Bu_4NNO_2 was used instead of Bu_4NBr.

We next examined the substrate scope in [3 + 2] cycloaddition under the optimized conditions shown in Table 1 (Table 2). There are no reports on successful copper-catalyzed [3 + 2] cycloadditions of styrenes and 2-bromoketoesters to obtain diarylated dihydrofuranes **3**; however, our copper-TPMA catalyst system realized the reaction of styrenes and 2-bromoketoesters to produce the corresponding [3 + 2] cycloadducts, dihydrofurans **3**, in moderate to good yields without isomers. 2-Bromoketoester derivatives **2** smoothly reacted with *p*-methoxystyrene **1a** and gave the products **3b**–**3k**. These results demonstrate the broad applicability of our protocol. Ketoester **2** possessing an adamantyl group gave the corresponding furan derivatives **3b** in 91% yield, and aromatic ketoesters possessing electron-donating or electron-withdrawing groups also afforded the products **3c**, **3d**, and **3e** in good yields. Ketoesters **2** possessing ortho-substituted aryl groups leading to **3h** and **3i** resulted in 78 and 83% yields; however, **2** possessing a more hindered mesityl group and two tert-butyl groups gave **3j** and **3k** in 73% and 60% yields, respectively. The reaction with alpha-methylstyrene resulted in 42% yield. The steric bulkiness of **2** tended to decrease the product yields.

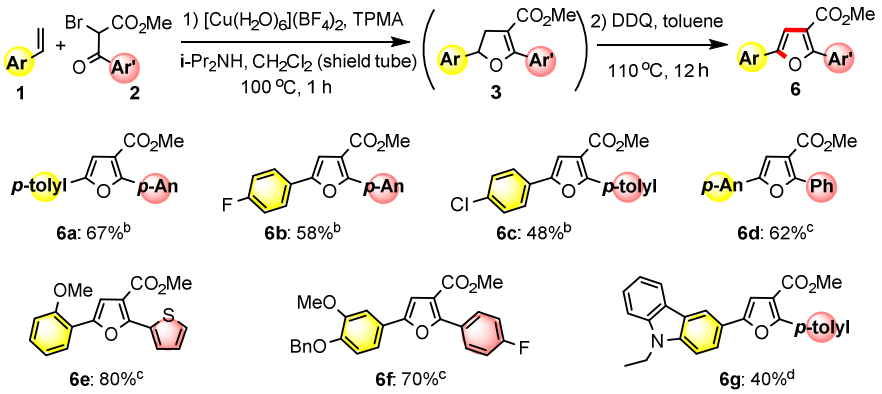
Table 2. Regioselective [3+2] cycloadditions



All reactions were carried out for 20 h at 80 °C in shield tubes with CH_2Cl_2 10 mol% $[Cu(II)(H_2O)_6](BF_4)_2$, *i*-Pr_2NH (1.5 equiv), TPMA (10 mol%), Bu_4N-NO_2 (20 mol%), **2** (1 equiv.) and **4** (2.0 equiv.). Pure compounds **5** were obtained by GPC and yields were determined by ^1H NMR because of inseparable dehalogenated starting material **4** from **5**. [a] (tris[2-(dimethylamino)ethyl]amine) (Me_6TREN, 10 mol%) was added.

Our next challenge is to develop the synthesis of diaryl-substituted furans **6** from the reaction of **1** and **2**. We attempted to oxidize the crude product **3** with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) to produce **6**. However, the reaction did not proceed smoothly to completion, and inseparable side products were also obtained after oxidation. Further reaction optimization conditions revealed that increases in the amount of **1** (or **2**) and the reaction temperature (100°C at 4 bar) were very effective for efficiently obtaining the [3+2]-cycloaddition product **3** in 1 h. The resulting crude product **3** reacted smoothly with DDQ to give the corresponding furan **6** in high yields. After the simple oxidation of the crude product **3** with DDQ, various furans **6** with ether, amine, and halogen functional groups (**6a-g**) were obtained in good yields without any isolation of **3**. (Scheme 4).

Scheme 4. Diaryl furan 6 synthesis.



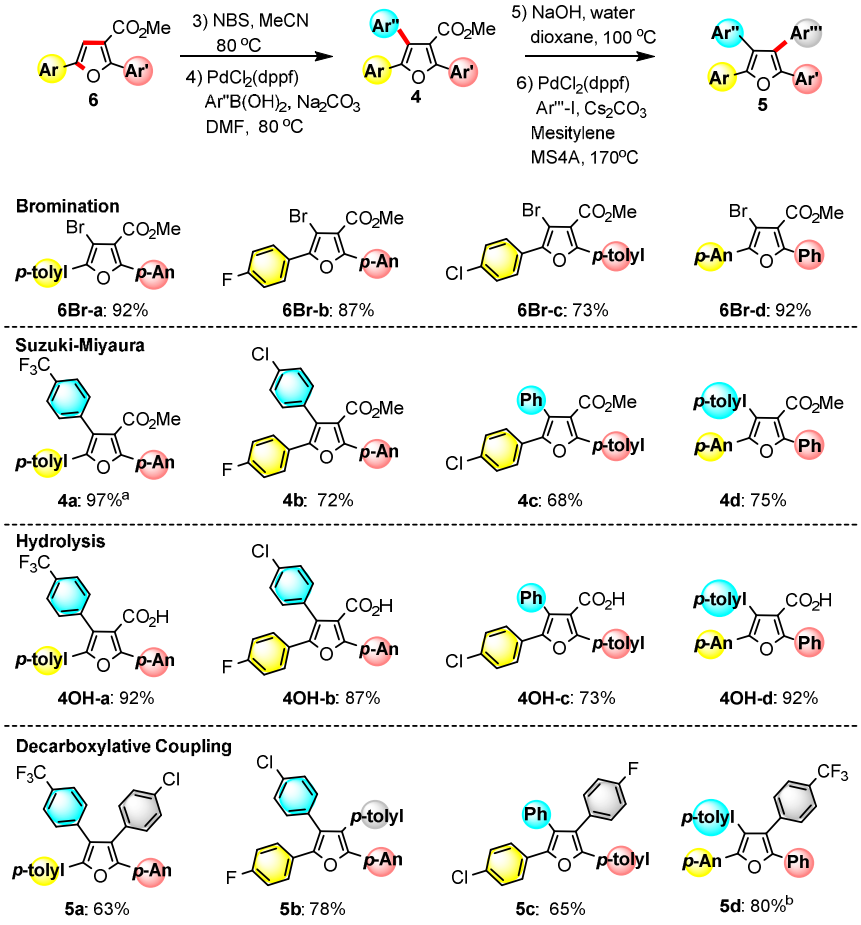
[a] Isolated yields for 2 steps. [b] 3 equiv of **1**. [c] 3 equiv of **2** was used. [d] 2 equiv of **2** was used.

The third arylation of **6** to give **4** was examined via 3) bromination with N-Bromosuccinimide (NBS) and 4) Suzuki–Miyaura couplings (Scheme 5). Although the bromination of **3** occurred smoothly to give the brominated furans (**6Br-a-d**), careful optimization of the following Suzuki–Miyaura couplings was required. The Suzuki–Miyaura coupling of highly bulky substrates is not easy[15]. We examined various conditions that included the modification of solvents, bases, and Pd catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and $PdCl_2(P(o\text{-}tolyl)_3)$. We discovered that $PdCl_2(dppf)$ (or $PdCl_2(t\text{-}Bu_2PC_6H_4(p\text{-}NMe_2))$) and $Na_2CO_3(aq)$ in DMF

were the best conditions (see SI). These established conditions were suitable for couplings between brominated furans **6Br** and representative arylboronic acids such as *p*-$CF_3C_6H_4$-, *p*-ClC_6H_4-, Ph, and *p*-$CH_3C_6H_4B(OH)_2$. Under optimized conditions, the trisubstituted furans that possess various aryl groups (**4a-d**) were obtained in good to excellent yields. We also attempted to obtain direct furan C–H arylations, but no reaction was observed.

Finally, the fourth arylation to obtain the desired tetraarylfuran **5** was conducted using 6) Pd-catalyzed decarboxylative coupling after the 5) hydrolysis of **4** (Scheme 5). The ester groups on the furan rings in **4** were smoothly hydrolyzed to give their corresponding carboxylic acids in high yields (**4OH-a-d**). Although there are some reports on decarboxylative couplings, couplings with sterically hindered aromatic groups have not been extensively investigated[4c, 16]. We further examined various reaction conditions with different solvents, additives, and Pd catalysts such as $Pd(OAc)_2$-PCy_3, $PdCl_2(t\text{-}Bu_2PC_6H_4(p\text{-}NMe_2))$, $PdCl_2(PPh_3)_2$, and $PdCl_2(DPEphos)_2$, (see SI). As a result, we developed an efficient decarboxylative coupling reaction of hydrolyzed **4** with aryl iodides such as *p*-ClC_6H_4-, *p*-$CH_3C_6H_4$-, *p*-FC_6H_4-, and *p*-$CF_3C_6H_4I$ in the presence of $PdCl_2$(dppf) in mesitylene at 170°C. We demonstrated that the styrenes **1** were successfully converted into various aryl substituted-furans **5c-5d** in a total of **6** steps (from styrene **1**) with good yields.

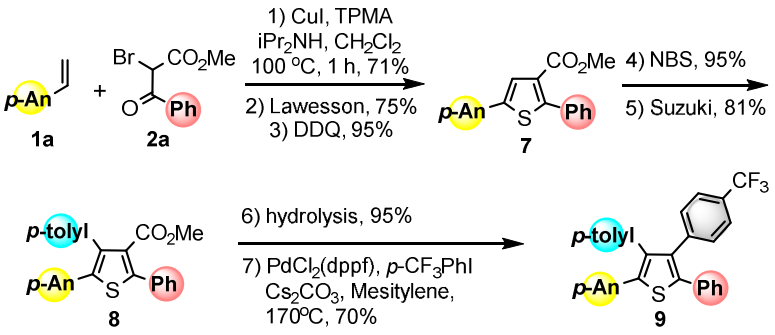
Scheme 5. Tri- and tetraarylfurans



[a]$PdCl_2(t\text{-}Bu_2PC_6H_4(p\text{-}NMe_2))$ was used. [b]$Pd(OAc)_2/PCy_3$ was used.

Our established protocol in this manuscript can be applied to the synthesis of a tetraarylated thiophene (scheme 6). The [3+2] cycloaddition reaction of **1a** and **2a** and a subsequent sulfur–oxygen exchange reaction with Lawesson's reagent[16] gave dihydrothiophene. The oxidation of dihydrothiophene with DDQ gave **7** without its regioisomer in a 48% yield after 3 steps. Triarylthiophene **8** was obtained after the bromination of **7** with NBS (95%) followed by Suzuki–Miyaura coupling (81%). The resulting product **8** was then subjected to hydrolysis followed by decarboxylative coupling with p-$CF_3C_6H_4$-I to produce tetraarylthiophene **9** in a 66% yield (2 steps).

Scheme 6. Tetraarylthiophene 9 synthesis



CONCLUSION

It is very difficult to selectively synthesize all of the various aryl-substituted furans. In this manuscript, our current protocol for the synthesis of these compounds involves a 1) Cu-catalyzed formal [3+2]-cycloaddition of styrenes **1** and bromoketoesters **2** to give diaryl-substituted dihydrofurans **3**, 2) DDQ oxidation of **3** to give diarylfurans **6**, 3) bromination of **6** to give brominated furans **6Br**, 4) Suzuki–Miyaura coupling to give triarylfurans **4**, 5) hydrolysis of **4** to give carboxylic acids **4OH**, and 6) decarboxylative couplings of **4OH** to give the desired tetraarylfurans **5**. Our protocol enabled the efficient installation of four different aryl groups onto the furan ring in 6 steps with perfect selectivities from widely available styrenes **1**. In addition, diaryl-substituted dihydrofurans **3** can easily be converted into dihydrothiophenes with Lawesson's reagent. After an oxygen–sulfur exchange, transformations that are similar to the reactions shown above can be applied to dihydrothiophene to obtain tetraarylthiophene **9** in 7 steps. These short sequences constitute a new and convenient method for the synthesis of **5** and **9**.

EXPERIMENTAL SECTION

General Information

All reactions were carried out under nitrogen (99.95%) atmosphere. For TLC analyses precoated Kieselgel 60 F254 plates (0.25 mm thick) were used; for column chromatography (40-63 μm) was used. Visualization was accomplished by UV light (254 nm), ^{1}H and ^{13}C NMR spectra were obtained using a 500 MHz NMR spectrometer. Chemical shifts for 1H NMR were described in parts per million (chloroform as an internal standard δ = 7.26) in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard (δ = 77.16), unless otherwise noted. High resolution mass analyses were obtained using a TOF-MS for ESI. Purification was performed by Gel Permeation Chromatography (GPC) System (Detector UV 254 nm).

Typical Experimental Procedure for Synthesis of 3a-3u

Cu salt (0.05 mmol), TPMA (0.05 mmol), and tetrabutylammonium nitrite (0.1 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap (or Biotage shield tube for microwave.). **1** (0.50 mmol), **2** (1.0 mmol), amine (0.75 mmol) and dried CH_2Cl_2 (2.0 mL) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere (charged by general N_2 (99.95%) gas flow) for 20 h at the temperature shown in tables. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product (**3a-3u**). Further purification was carried out by using GPC.

Typical Experimental Procedure for Synthesis of 4a-4d

Pd cat. (5 mol%), bromide **6Br** (1 equiv.), and boronic acid (2 equiv.) were added under air to a dram vial equipped with a stir bar and a screw cap. DMF and 2M Na_2CO_3 aq. (2 mL/mmol, 4 equiv.) were added to the mixture under nitrogen atmosphere (charged by general N_2 (99.95%) gas flow) and the reaction mixture was stirred at 80 ^{o}C for 12 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc and GPC (Gel Permeation Chromatography) to afford the product (**4a-4d**).

Typical Experimental Procedure for Synthesis of 4OH-a-4OH-d

Ester (0.25 mmol, 1 equiv.) in 0.5 M NaOH aq. (2 eqiv. 4 mL/mmol) and Dioxane was stirred at 100 ^{o}C for 12 hr. At this time, the mixture was acidified by conc. HCl aq. and

extracted with EtOAc to afford the carboxylic acid (**4OH-a-4OH-d**).

Typical Experimental Procedure for Synthesis of 5a-5d

Pd cat. (10 mol%), carboxylic acid **4OH** (0.25 mmol, 1 equiv.), iodide (2 equiv.), Cs_2CO_3 (3 equiv.) MS4A (300 mg/mmol) were added under air to a dram vial equipped with a stir bar and a screw cap. Mesitylene was added to the mixture under nitrogen atmosphere (charged by general N_2 (99.95%) gas flow) and the reaction mixture was stirred at 170 ^oC for 12 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc and GPC (Gel Permeation Chromatography) to afford the product (**5a-5d**).

Typical Experimental Procedure for Synthesis of 6Br-a-6Br-g

Furan **6** (1 equiv.) and NBS (1.05 equiv.) and CH_3CN were added to a dram vial equipped with a stir bar and a screw cap and the resulting mixture was stirred at 50 ^oC for 12 h. After this time, the contents of the flask were concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the bromide (**6Br-a-6Br-g**)**.**

Typical Experimental Procedure for Synthesis of 6a-6g

Cu salt (0.05 mmol) was added under air to a dram vial equipped with a stir bar and a screw cap. **1** (1.50 mmol), **2** (0.50 mmol), amine (0.75 mmol), ligand (0.05 mmol) and dried CH_2Cl_2 (2.0 mL) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere (charged by general N_2 (99.95%) gas flow) at 100 ^oC for 1 h (The ratio of **1** and **2** was shown in each compound analysis). After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue dissolved in toluene was taken into a dram vial equipped with a stir bar and a screw cap. DDQ (0.60 mmol) was added and the reaction mixture was stirred at 110 ^oC for 12 h. After this time, the contents of the flask were concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **6**.

Methyl 2-(tert-butyl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (3a). Pale yellow oil (82%, 119mg), **IR** (neat) ν 2951, 1700, 1598, 1512, 1238, 1099 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 2.91 (dd, *J* = 8.3 and 14.5 Hz, 1H), 3.33 (dd, *J* = 10.9 and 14.5 Hz, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 5.45 (dd, *J* = 8.3 and 10.9 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.7, 34.6, 40.1, 50.8, 55.4, 81.7, 99.1, 114.1, 127.0, 134.3, 159.5, 165.9, 177.4. **HRESIMS** calcd. for $C_{17}H_{22}O_4Na$ ($M+Na^+$): 313.1494; found 313.1490.

Methyl 2-(1-adamantanyl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate

(3b). Pale yellow oil (91%, 168mg), **IR** (neat) ν 2901, 2848, 1699, 1592, 1512, 1241, 1173, 1074, 1033 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.69-1.78 (m, 6H), 3.12 (brs, 3H), 2.12 (brs, 6H), 2.90 (dd, *J* = 8.4 and 14.6 Hz, 1H), 3.33 (dd, *J* = 10.9 and 14.6 Hz, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 5.43 (dd, *J* = 8.4 and 10.9 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 28.5, 36.8, 37.1, 38.2, 40.1, 50.9, 55.4, 81.5, 99.1, 114.2, 127.1, 134.5, 159.6, 166.0, 177.4. **HRESIMS** calcd. for $C_{23}H_{29}O_4$ ($M+H^+$): 369.2066; found 369.2074.

Methyl 2,5-bis(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (3c).

Pale yellow oil (84%, 143mg), **IR** (neat) ν 2947, 1694, 1680, 1606, 1511, 1242, 1175, 1081, 1032 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.10 (dd, *J* = 8.7 and 15.1 Hz, 1H), 3.47 (dd, *J* = 10.6 and 15.1 Hz, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 5.62 (dd, *J* = 8.7 and 10.6 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 39.6, 51.1, 55.4, 55.4, 82.4, 100.4, 113.2, 114.2, 122.3, 127.5, 131.4, 133.8, 159.8, 161.5, 165.1, 166.1. **HRESIMS** calcd. for $C_{20}H_{20}O_5Na$ ($M+Na^+$): 363.1231; found 363.1208.

Methyl 5-(4-methoxyphenyl)-2-phenyl-4,5-dihydrofuran-3-carboxylate (3d). Pale yellow oil (80%, 124mg), **IR** (neat) ν 2948, 1705, 1514, 1244, 1088 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.13 (dd, *J* = 8.7 and 15.2 Hz, 1H), 3.51 (dd, *J* = 10.7 and 15.2 Hz, 1H), 3.66 (s, 3H), 3.79 (s, 3H), 5.66 (dd, *J* = 8.7 and 10.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.36-7.42 (m, 3H), 7.82 (dd, *J* = 1.7 and 8.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 39.7, 51.1, 55.4, 82.7, 101.8, 114.2, 127.5, 127.8, 129.5, 130.0, 130.6, 133.6, 159.8, 165.2, 165.8. **HRESIMS** calcd. for $C_{19}H_{18}O_4Na$ ($M+Na^+$): 333.1103; found 333.1097.

Methyl 2-(4-bromophenyl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate(3e). Pale yellow oil (99%, 193mg), **IR** (neat) ν 2946, 1700, 1610, 1512, 1238, 1081 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.12 (dd, *J* = 8.7 and 15.3 Hz, 1H), 3.48 (dd, *J* = 10.7 and 15.3 Hz, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 5.55 (dd, *J* = 8.7 and 10.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 39.6, 51.2, 55.3, 82.7, 102.47, 114.2, 125.0, 127.4, 128.8, 131.0, 131.1, 133.3, 159.8, 163.8, 165.6. **HRESIMS** calcd. for $C_{19}H_{17}O_4BrNa$ ($M+Na^+$): 411.0208; found 411.0210.

Methyl 5-(4-methoxyphenyl)-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (3f). Pale yellow oil (77%, 122mg), **IR** (neat) ν 2946, 1691, 1597, 1511, 1239, 1174, 1072, 1030 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.10 (dd, *J* = 8.4 and 15.4 Hz, 1H), 3.49 (dd, *J* = 10.5 and 15.4 Hz, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 5.64 (dd, *J* = 8.4 and 10.5 Hz, 1H),

6.88 (dd, *J* = 8.6 Hz, 2H), 7.09 (dd, *J* = 3.8 and 5.1 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 1.2 and 5.1 Hz, 1H), 8.22 (d, *J* = 3.7 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 39.8, 51.1, 55.3, 82.4, 100.0, 114.1, 127.2, 127.3, 130.4, 131.4, 132.5, 133.55, 158.67, 159.7, 165.7. **HRESIMS** calcd. for $C_{17}H_{16}O_4SNa$ ($M+Na^+$): 339.0667; found 339.0671.

Methyl 5-(4-methoxyphenyl)-4,5-dihydro-[2,2'-bifuran]-3-carboxylate (3g). Pale yellow oil (76%, 114mg), **IR** (neat) ν 2947, 1690, 1652, 1513, 1231, 1089, 1027 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.11 (dd, *J* = 8.7 and 15.5 Hz, 1H), 3.45 (dd, *J* = 10.5 and 14.6 Hz, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 5.67 (dd, *J* = 8.7 and 10.5 Hz, 1H), 6.51 (dd, *J* = 1.8 and 3.5 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 3.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 39.3, 51.3, 55.5, 83.3, 100.8, 112.1, 114.3, 114.3, 118.0, 127.7, 133.2, 144.4, 144.5, 154.7, 160.0, 165.3. **HRESIMS** calcd. for $C_{17}H_{16}O_5Na$ ($M+Na^+$): 323.0895; found 323.0900.

Methyl 5-(4-methoxyphenyl)-2-(o-tolyl)-4,5-dihydrofuran-3-carboxylate (3h). Pale yellow oil (78%, 127mg), **IR** (neat) ν 2947, 1685, 1636, 1513, 1436, 1235, 1077, 1030 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 3.16 (dd, *J* = 8.9 and 15.0 Hz, 1H), 3.49 (dd, *J* = 10.7 and 15.0 Hz, 1H), 3.57 (s, 3H), 3.79 (s, 3H), 5.72 (dd, *J* = 8.9 and 10.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.18-7.21 (m, 2H), 7.28 (dt, *J* = 1.4 and 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 19.7, 38.3, 51.1, 55.4, 83.8, 114.3, 125.3, 127.7, 129.6, 129.8, 130.2, 130.7, 133.4, 137.0, 159.9, 165.6, 166.6. **HRESIMS** calcd. for $C_{20}H_{20}O_4Na$ ($M+Na^+$): 347.1259; found 347.1267.

Methyl 2-(2-bromophenyl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (3i). Pale yellow oil (83%, 162mg), **IR** (neat) ν 2947, 1690, 1652, 1513, 1231, 1089, 1027 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.16 (dd, *J* = 9.2 and 15.2 Hz, 1H), 3.50 (dd, *J* = 10.7 and 15.2 Hz, 1H), 3.58 (s, 3H), 3.81 (s, 3H), 5.76 (dd, *J* = 9.2 and 10.7 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.24 (m, 1H), 7.32 (dt, *J* = 0.9 and 7.5 Hz, 1H), 7.39 (dd, *J* = 1.8 and 7.5 Hz, 1H), 7.41 (dd, *J* = 0.9 and 8.0 Hz, 2H), 7.61 (d, *J* = 0.9 and 8.7 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 38.4, 51.2, 55.5, 84.6, 105.4, 114.3, 122.7, 127.1, 128.0, 131.0, 131.0, 132.9, 133.2, 160.0, 164.5, 165.3. **HRESIMS** calcd. for $C_{19}H_{17}O_4BrNa$ ($M+Na^+$): 411.0208; found 411.0217.

Methyl 2-mesityl-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (3j). Pale yellow oil (73%, 129mg), **IR** (neat) ν 2948, 1685, 1637, 1513, 1436, 1230, 1076, 1031 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.18 (s, 3H), 2.25 (s, 6H), 3.16 (dd, *J* = 9.4 and 14.8 Hz, 1H), 3.45 (dd, *J* = 10.7 and 14.8 Hz, 1H), 3.54 (s, 3H), 3.79 (s, 3H), 5.72 (dd, *J* = 9.4 and 10.7 Hz, 1H), 6.82 (s, 1H), 6.84 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 19.6, 21.3, 37.8, 51.0, 55.4, 83.8, 104.8, 114.2, 127.9, 127.94, 128.1, 128.1, 133.3, 136.2, 136.5, 138.8, 159.8, 165.5, 1664. **HRESIMS**

calcd. for $C_{22}H_{24}O_4Na$ ($M+Na^+$): 375.1572; found 375.1578.

1-(2-(tert-Butyl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-yl)-2,2-dimethylpropan-1-one (3k). Pale yellow oil (60%, 95mg), **IR** (neat) ν 2959, 1514, 1248, 902 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.14 (s, 9H), 1.18 (s, 9H), 2.98 (dd, *J* = 9.1 and 13.8 Hz, 1H), 3.33 (dd, *J* = 10.3 and 13.8 Hz, 1H), 3.79 (s, 3H), 5.38 (dd, *J* =9.1 and 10.3 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.3, 28.4, 34.2, 43.2, 44.2, 55.4, 81.4, 108.0, 114.1, 127.0, 134.5, 159.5, 169.2, 209.4. **HRESIMS** calcd. for $C_{20}H_{29}O_3$ ($M+H^+$): 317.2117; found 317.2109.

Methyl 2-(tert-butyl)-5-(p-tolyl)-4,5-dihydrofuran-3-carboxylate (3l). Pale yellow oil (85%, 117mg), **IR** (neat) ν 2950, 1701, 1599, 1238, 1100 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.36 (s, 9H), 2.34 (s, 3H), 2.91 (dd, *J* = 8.2 and 14.5 Hz, 1H), 3.34 (dd, *J* = 10.9 and 14.5 Hz, 1H), 3.66 (s, 3H), 5.47 (dd, *J* = 8.2 and 10.9 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.8, 27.7, 34.6, 40.1, 50.8, 81.7, 99.1, 125.5, 129.4, 137.8, 139.3, 165.8, 177.4. **HRESIMS** calcd. for $C_{17}H_{22}O_3Na$ ($M+Na^+$): 297.1467; found 297.1473.

Methyl 2-(tert-butyl)-5-(o-tolyl)-4,5-dihydrofuran-3-carboxylate (3m). Pale yellow oil (54%, 74mg), **IR** (neat) ν 2951, 1701, 1599, 1238, 1101 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 2.31 (s, 3H), 2.79 (dd, *J* = 8.7 and 14.3 Hz, 1H), 3.40 (dd, *J* = 11.1 and 14.3 Hz, 1H), 3.67 (s, 3H), 5.68 (dd, *J* = 8.7 and 11.1 Hz, 1H), 7.17-7.24 (m, 3H), 7.30-7.32 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 19.2, 27.7, 34.7, 39.3, 50.8, 79.6, 99.0, 124.2, 126.2, 127.6, 130.6, 134.1, 140.2, 165.7, 177.4. **HRESIMS** calcd. for $C_{17}H_{22}O_3Na$ ($M+Na^+$): 297.1467; found 297.1465.

Methyl 2-(tert-butyl)-5-phenyl-4,5-dihydrofuran-3-carboxylate (3n). Pale yellow oil (56%, 73mg), **IR** (neat) ν 2951, 1701, 1599, 1238, 1100 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.36 (s, 9H), 2.90 (dd, *J* = 8.2 and 14.5 Hz, 1H), 3.34 (dd, *J* = 11.0 and 14.5 Hz, 1H), 3.67 (s, 3H), 5.47 (dd, *J* = 8.2 and 11.0 Hz, 1H), 7.29-7.31 (m, 3H), 7.35-7.38 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.7, 34.7, 40.2, 50.9, 81.7, 125.4, 128.0, 128.8, 142.3, 165.8, 177.4. **HRESIMS** calcd. for $C_{16}H_{20}O_3Na$ ($M+Na^+$): 283.1310; found 283.1315.

Methyl 2-(tert-butyl)-5-(4-fluorophenyl)-4,5-dihydrofuran-3-carboxylate (3o). Pale yellow oil (62%, 86mg), **IR** (neat) ν 2952, 1701, 1601, 1509, 1238, 1101 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 2.91 (dd, *J* = 8.3 and 14.5 Hz, 1H), 3.33 (dd, *J* = 10.9 and 14.5 Hz, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 5.45 (dd, *J* = 8.3 and 10.9 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 2H), 7.28 (dd, *J* = 5.2 and 8.7 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.7, 34.6, 40.2, 50.9, 81.4, 99.1, 115.7 (d, *J* = 21.5 Hz), 127.3 (d, *J* = 8.2 Hz), 138.1 (d, *J* = 3.2 Hz), 162.0 (d, *J* = 246.2 Hz), 165.7, 177.2. **HRESIMS** calcd. for $C_{16}H_{19}O_3FNa$

(M+Na^+): 301.1216; found 301.1211.

Methyl 2-(tert-butyl)-5-(4-chlorophenyl)-4,5-dihydrofuran-3-carboxylate (3p). Pale yellow oil (82%, 121mg), **IR** (neat) ν 2950, 1701, 1601, 1238, 1100 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 2.87 (dd, *J* = 8.2 and 14.6 Hz, 1H), 3.35 (dd, *J* = 11.0 and 14.6 Hz, 1H), 3.67 (s, 3H), 5.47 (dd, *J* = 8.2 and 11.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.7, 34.6, 40.2, 50.9, 80.9, 99.23, 126.9, 128.9, 133.8, 140.8, 165.7, 177.2. **HRESIMS** calcd. for $C_{16}H_{19}O_3ClNa$ (M+Na^+): 317.0920; found 317.0927.

Methyl 2-(tert-butyl)-5-(2-chlorophenyl)-4,5-dihydrofuran-3-carboxylate (3q). Pale yellow oil (51%, 75mg), **IR** (neat) ν 2951, 1702, 1606, 1239, 1101 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.40 (s, 9H), 2.76 (dd, *J* = 8.0 and 14.8 Hz, 1H), 3.53 (dd, *J* = 11.2 and 14.8 Hz, 1H), 3.65 (s, 3H), 5.79 (dd, *J* = 8.0 and 11.2 Hz, 1H), 7.23 (dt, *J* = 1.8 and 7.5 Hz, 1H), 7.28 (dt, *J* = 1.2 and 7.5 Hz, 1H), 7.35 (dt, *J* = 1.6 and 9.2 Hz, 2H),. **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.8, 34.7, 39.6, 50.9, 78.8, 99.3, 125.8, 127.1, 128.9, 129.8, 131.3, 140.2, 165.7, 177.1. **HRESIMS** calcd. for $C_{16}H_{19}O_3ClNa$ (M+Na^+): 317.0920; found 317.0914.

Methyl 5-(4-bromophenyl)-2-(tert-butyl)-4,5-dihydrofuran-3-carboxylate (3r). Pale yellow oil (81%, 137mg), **IR** (neat) ν 2951, 1701, 1602, 1239, 1100 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 2.87 (dd, *J* = 8.1 and 14.5 Hz, 1H), 3.35 (dd, *J* = 10.0 and 14.5 Hz, 1H), 3.67 (s, 3H), 5.46 (dd, *J* = 8.1 and 10.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.7, 34.6, 40.1, 50.9, 80.9, 99.1, 121.8, 127.1, 131.8, 141.2, 165.5, 177.0. **HRESIMS** calcd. for $C_{16}H_{19}O_3BrNa$ (M+Na^+): 361.0415; found 361.0420.

Methyl 2-(tert-butyl)-5-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (3s). Pale yellow oil (42%, 58mg), **IR** (neat) ν 2951, 1702, 1600, 11242, 1107, 1017 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.34 (s, 9H), 3.04 (d, *J* = 4.3 Hz, 1H), 3.13 (d, *J* = 4.3 Hz, 1H), 3.61 (s, 3H), 7.20-7.24 (m, 1H), 7.32 (d, *J* = 4.8 Hz, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 27.6, 29.5, 34.7, 46.1, 50.8, 86.8, 98.7, 124.3, 127.2, 128.5, 147.0, 165.9, 176.3. **HRESIMS** calcd. for $C_{17}H_{22}O_3Na$ (M+Na^+): 297.1467; found 297.1465.

Methyl 2-(4-methoxyphenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-3-carboxylate (4a). White solid (97%, 113mg), **Mp:** 169 – 170 °C, **IR** (neat) ν 2952, 1717, 1615, 1500, 1331, 1116 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.59 (s, 3H), 3.89 (s, 3H), 6.97 – 7.03 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.84 – 7.89 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.3, 51.5, 55.4, 113.8, 114.8, 121.6, 122.4, 124.4 (q, *J* = 273.0 Hz), 125.4 (q, *J* = 3.9 Hz), 126.0, 126.9, 129.3, 129.7 (d, *J* = 32.0 Hz), 129.8, 130.6, 137.6 (q, *J* = 1.0

Hz), 138.2, 148.7, 155.6, 160.6, 164.6. **HRESIMS** calcd. for $C_{27}H_{22}F_3O_4$ ($M+H^+$): 467.1470; found 467.1480.

Methyl 4-(4-chlorophenyl)-5-(4-fluorophenyl)-2-(4-methoxyphenyl)furan-3-carboxylate (4b). White solid (72%, 79mg), **Mp:** 120 – 121 °C, **IR** (neat) ν 2960, 1704, 1607, 1499, 1228, 829 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.60 (s, 3H), 3.88 (s, 3H), 6.67 – 7.01 (m, 4H), 7.27 – 7.30 (m, 2H), 7.33 – 7.37 (m, 2H), 7.38 – 7.41 (m, 2H), 7.82 – 7.86 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.5, 55.4, 113.9, 115.0, 115.7 (d, *J* = 21.8 Hz), 122.1, 122.3, 126.2 (d, *J* = 3.1 Hz), 127.8 (d, *J* = 8.1 Hz), 128.9, 129.7, 131.5, 131.8, 133.8, 147.5, 155.7, 160.7, 162.4 (d, *J* = 248.6 Hz), 164.6. **HRESIMS** calcd. for $C_{25}H_{18}ClFNaO_4$ ($M+Na^+$): 459.0775; found 459.0769.

Methyl 5-(4-chlorophenyl)-4-phenyl-2-(p-tolyl)furan-3-carboxylate (4c). Colorless oil (68%, 68mg), **IR** (neat) ν 2947, 1717, 1590, 1500, 820 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.59 (s, 3H), 7.19 – 7.23 (m, 2H), 7.25 – 7.30 (m, 2H), 7.31 – 7.37 (m, 4 H), 7.39 – 7.44 (m, 3H), 7.77 (d, *J* = 8.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.6, 51.6, 116.2, 124.2, 126.0, 127.2, 128.0, 128.0, 128.7, 128.8, 129.3, 130.0, 133.0, 133.7, 139.7, 147.3, 155.3, 164.8. **HRESIMS** calcd. for $C_{25}H_{19}ClNaO_3$ ($M+Na^+$): 425.0920; found 425.0917.

Methyl 5-(4-methoxyphenyl)-2-phenyl-4-(p-tolyl)furan-3-carboxylate (4d). White solid (75%, 75mg), **Mp:** 127 – 128 °C, **IR** (neat) ν 2951, 1720, 1606, 1492 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 3.62 (s, 3H), 3.78 (s, 3H), 6.76 – 6.83 (m, 2H), 7.18 – 7.28 (m, 4H), 7.35 – 7.42 (m, 3H), 7.42 – 7.49 (m, 2H), 7.81 – 7.89 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.3, 51.5, 55.2, 113.8, 116.5, 122.1, 123.0, 127.4, 127.6, 128.3, 128.9, 129.2, 129.8, 130.0, 130.1, 137.2, 148.6, 153.7, 159.2, 165.0. **HRESIMS** calcd. for $C_{26}H_{23}O_4$ ($M+H^+$): 399.1596; found 399.1596.

2-(4-Methoxyphenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-3-carboxylic acid (4OH-a). White solid (92%, 104mg), **IR** (neat) ν 2917, 1674, 1609, 1498, 1440, 1328, 1112 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 1.51 (s, 3H), 3.08 (s, 3H), 6.30 – 6.34 (m, 2H), 6.39 (d, *J* = 8.2 Hz, 2H), 6.48 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 7.09 – 7.14 (m, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 20.8, 55.3, 114.0, 115.9, 121.4, 121.7, 124.4 (q, *J* = 273.7 Hz), 125.3 (q, *J* = 4.0 Hz), 125.8, 126.4, 128.1 (d, *J* = 31.5 Hz), 129.2, 129.4, 130.8, 137.5 (q, *J* = 1.9 Hz), 138.0, 147.8, 153.5, 160.1, 164.8. **HRESIMS** calcd. for $C_{26}H_{19}F_3NaO_4$ ($M+Na^+$): 475.1133; found 475.1126.

4-(4-Chlorophenyl)-5-(4-fluorophenyl)-2-(4-methoxyphenyl)furan-3-carboxylic acid (4OH-b). White solid (87%, 92mg), **IR** (neat) ν 3075, 1674, 1606, 1501, 1441, 833 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 3.08 (s, 3H), 6.29 – 6.33 (m, 2H), 6.41 – 6.46 (m, 2H), 6.59 – 6.67 (m, 4H), 6.71 – 6.75 (m, 2H), 7.09 – 7.13 (m, 2H). **^{13}C NMR** (125 MHz,

DMSO-d_6) δ: 55.3, 114.1, 115.9 (d, *J* = 21.9 Hz), 116.2, 121.7, 122.0, 126.0 (d, *J* = 3.0 Hz), 127.9 (d, *J* = 8.4 Hz), 128.7, 129.2, 131.7, 131.8, 132.6, 146.5, 153.5, 160.2, 161.8 (d, *J* = 246.3 Hz), 164.9. **HRESIMS** calcd. for $C_{24}H_{16}ClFNaO_4$ ($M+Na^+$): 445.0619; found 445.0621.

5-(4-Chlorophenyl)-4-phenyl-2-(p-tolyl)furan-3-carboxylic acid (4OH-c). White solid (73%, 71mg), **IR** (neat) ν 3219, 1681, 1613, 1480, 1445, 827 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 1.53 (s, 3H), 6.46 – 6.63 (m, 11H), 6.95 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 20.9, 117.7, 124.0, 126.5, 127.0, 127.2, 128.1, 128.4, 128.7, 128.8, 129.3, 129.7, 132.3, 132.7, 139.1, 146.3, 152.5, 165.1. **HRESIMS** calcd. for $C_{24}H_{17}ClNaO_3$ ($M+Na^+$): 411.0764; found 411.0773.

5-(4-Methoxyphenyl)-2-phenyl-4-(p-tolyl)furan-3-carboxylic acid (4OH-d). White solid (92%, 88mg), **IR** (neat) ν 2918, 1687, 1606, 1487 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ: 1.51 (s, 3H), 2.89 (s, 3H), 6.01 – 6.10 (m, 2H), 6.35 – 6.41 (m, 4H), 6.47 – 6.52 (m, 2H), 6.56 – 6.62 (m, 1H), 6.62 – 6.69 (m, 2H), 7.01 (d, *J* = 7.4 Hz, 2H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ: 20.9, 55.2, 114.2, 118.3, 121.7, 122.2, 126.7, 127.2, 128.7, 128.9, 129.3, 129.5, 129.6, 129.7, 137.0, 147.9, 150.9, 159.2, 165.5. **HRESIMS** calcd. for $C_{25}H_{21}O_4$ ($M+H^+$): 385.1440; found 385.1446.

3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan (5a). White solid (63%, 82mg), **Mp:** 186 – 187 °C, **IR** (neat) ν 2931, 1612, 1508, 1320, 1254, 831 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 3.80 (s, 3H), 6.81 – 6.85 (m, 2H), 7.02 – 7.07 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.26 (m, 4H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.43 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.4, 55.4, 114.1, 121.8, 122.6, 123.3, 124.3 (q, *J* = 272.0 Hz), 125.6 (q, *J* = 4.0 Hz), 126.2, 127.6, 127.6, 129.0, 129.4, 130.8, 131.6, 131.8, 133.4, 137.2 (q, *J* = 1.7 Hz), 137.9, 148.4, 159.3. **HRESIMS** calcd. for $C_{31}H_{22}ClF_3NaO_2$ ($M+Na^+$): 541.1158; found 541.1160.

3-(4-Chlorophenyl)-2-(4-fluorophenyl)-5-(4-methoxyphenyl)-4-(p-tolyl)furan (5b). White solid (78%, 91mg), **Mp:** 178 – 179 °C, **IR** (neat) ν 2954, 1594, 1493, 1223, 828 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 3.80 (s, 3H), 6.79 – 6.84 (m, 2H), 6.94 – 7.02 (m, 4H), 7.04 – 7.09 (m, 4H), 7.20 – 7.25 (m, 2H), 7.41 – 7.47 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.4, 55.4, 114.0, 115.7 (d, *J* = 21.7 Hz), 123.4, 123.6, 123.7, 127.2, (d, *J* = 3.1 Hz), 128.7, 128.9, 129.5, 130.0, 130.4, 130.6, 131.8, 132.0, 133.3, 137.1, 146.7, 148.2, 159.2, 162.2 (d, J = 247.5 Hz). **HRESIMS** calcd. for $C_{30}H_{23}ClFO_2$ ($M+H^+$): 469.1371; found 469.1374.

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-3-phenyl-5-(p-tolyl)furan (5c). White solid (65%, 71mg), **Mp:** 190 – 192 °C, **IR** (neat) ν 2914, 1597, 1492, 1217, 819 cm^{-1}. **^{1}H NMR**

(500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 6.91 – 6.70 (m, 2H), 7.06 – 7.17 (m, 6H), 7.20 – 7.29 (m, 5H), 7.35 – 7.44 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.5, 115.7, 115.8, 123.7, 126.2, 127.2, 127.7, 128.0, 128.9, 129.3 (d, *J* = 3.3 Hz), 129.5, 129.6, 130.5, 130.7, 132.3 (d, *J* = 8.1 Hz), 133.2 (d, *J* = 21.1 Hz), 137.9, 146.7, 148.7, 162.4 (d, *J* = 246.2 Hz). **HRESIMS** calcd. for $C_{29}H_{21}ClFO$ ($M+H^+$): 439.1265; found 439.1262.

2-(4-Methoxyphenyl)-5-phenyl-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan (5d) White solid (80%, 97mg), **Mp:** 218 – 219 °C, **IR** (neat) ν 2925, 1605, 1496, 1327 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.79 (s, 3H), 6.78 – 6.85 (m, 2H), 6.98 – 7.02 (m, 2H), 7.04 – 7.08 (m, 2H), 7.21 – 7.31 (m, 5H). 7.42 – 7.51 (m, 10 H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.2, 55.2, 113.9, 123.1, 124.3 (q, *J* = 273 Hz), 123.6, 125.3 (q, *J* = 4 Hz), 126.1, 127.4, 127.6, 128.5, 129.1, (q, *J* = 33 Hz), 129.4, 129.7, 130.2, 130.6, 130.7, 137.0, 137.4, 147.7, 148.3, 159.1. **HRESIMS** calcd. for $C_{31}H_{24}F_3O_2$ ($M+H^+$): 485.1728; found 485.1724.

Methyl 2-(4-methoxyphenyl)-5-(p-tolyl)furan-3-carboxylate (6a). White solid (67%, 108mg), **Mp:** 120 – 121 °C, **IR** (neat) ν 2950, 1720, 1605, 1494, 1090, 1028, 834, 768 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.97 – 7.02 (m, 2H), 7.00 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 8.04 – 8.09 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.5, 51.7, 55.5, 107.1, 113.7, 114.1, 122.6, 124.0, 127.3, 129.6, 130.0, 138.0, 152.1, 156.7, 160.5, 164.3. **HRESIMS** calcd. for $C_{20}H_{18}NaO_4$ ($M+Na^+$): 345.1103; found 345.1101.

Methyl 5-(4-fluorophenyl)-2-(4-methoxyphenyl)furan-3-carboxylate (6b). White solid (58%, 95mg), **Mp:** 165 – 166 °C, **IR** (neat) ν 2959, 1722, 1588, 1495, 1215, 1088, 1026, 834, 769 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 3.88(s, 3H), 6.97 – 7.01 (m, 2H), 7.00 (s, 1H), 7.09 – 7.14 (m, 2H), 7.67 – 7.72 (m, 2H), 8.03 – 8.07 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.7, 55.3, 107.4 (d, *J* = 1.3 Hz), 113.7, 114.1, 115.9 (d, *J* = 22.0 Hz), 122.3, 125.7 (d, *J* = 8.0 Hz), 126.2 (d, *J* = 3.4 Hz), 129.9, 150.8, 156.9, 160.6, 162.4 (d, *J* = 248.0 Hz), 164.0. **HRESIMS** calcd. for $C_{19}H_{16}FO_4$ ($M+H^+$): 327.1033; found 327.1036.

Methyl 5-(4-chlorophenyl)-2-(p-tolyl)furan-3-carboxylate (6c). White solid (48%, 78mg), **Mp:** 103 – 104 °C, **IR** (neat) ν 2980, 2936, 1714, 1463 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.86 (s, 3H), 7.07 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.37 – 7.41 (m, 2H), 7.63 – 7.68 (m, 2H), 7.96 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.6, 51.8, 108.4, 115.1, 125.3, 126.9, 128.4, 128.5, 129.1, 129.2, 133.9, 140.0, 151.1, 157.4, 164.1. **HRESIMS** calcd. for $C_{19}H_{16}ClO_3$ ($M+H^+$): 327.0788; found 327.0787.

Methyl 2-phenyl-5-(p-tolyl)furan-3-carboxylate (6d). White solid (62%, 91mg), **Mp:** 88 – 89 °C, **IR** (neat) ν 2949, 1719, 1596, 1486, 754 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ:

3.85 (s, 3H), 3.86 (s, 3H), 6.95 (s, 1H), 6.92 – 6.99 (m, 2H), 7.38 – 7.43 (m, 1H), 7.64 – 7.70 (m, 2H), 8.03 – 8.09 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.6, 55.3, 106.2, 114.3, 115.4, 122.8, 125.5, 128.2, 128.2, 129.2, 129.9, 152.6, 156.1, 159.7, 164.2. **HRESIMS** calcd. for $C_{19}H_{17}O_4$ ($M+H^+$): 309.1127; found 309.1131.

Methyl 5-(2-methoxyphenyl)-2-(thiophen-2-yl)furan-3-carboxylate (6e). Yellow solid (80%, 126mg), **Mp:** 102 - 103 °C, **IR** (neat) ν 2942, 1704, 1579, 1489, 1248, 1094 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.92 (s, 3H), 3.99 (s, 3H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.03 – 7.10 (m, 1H), 7.14 (dd, *J* = 3.9 and 5.1 Hz, 1H), 7.27 – 7.32 (m, 2H), 7.45 (dd, *J* = 1.1 and 4.9 Hz, 1H), 7.9 (dd, *J* = 1.5 and 7.7 Hz, 1H), 8.14 (dd, *J* = 1.1 and 3.7 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.7, 55.6, 111.1, 112.3, 114.0, 118.6, 120.9, 126.1, 127.7, 128.0, 128.9, 132.0, 148.4, 151.4, 156.0, 164.3. **HRESIMS** calcd. for $C_{17}H_{14}NaO_4S$ ($M+Na^+$): 337.0511; found 337.0514.

Methyl 5-(4-(benzyloxy)-3-methoxyphenyl)-2-(4-fluorophenyl)furan-3-carboxylate (6f). White solid (70%, 151mg), **Mp:** 140 - 141 °C, **IR** (neat) ν 2952, 1721, 1600, 1497, 1214, 1097 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 3.97 (s, 3H), 5.21 (s, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.95 (s, 1H), 7.12 – 7.18 (m, 2H), 7.21 – 7.26 (m, 2H), 7.30 – 7.35 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 2H), 8.04 – 8.11 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.8, 56.3, 71.2, 106.7, 107.9, 114.3, 115.3, 115.5 (d, *J* = 21.8 Hz), 117.1, 123.4, 126.2 (d, *J* = 3.3 Hz), 127.5, 128.2, 128.8, 130.5 (d, *J* = 8.5 Hz), 137.0, 148.6, 150.1, 152.6, 155.5, 163.4 (d, *J* = 250.2 Hz), 164.2. **HRESIMS** calcd. for $C_{26}H_{21}FNaO_5$ ($M+Na^+$): 455.1271; found 455.1266.

Methyl 5-(9-ethyl-9H-carbazol-3-yl)-2-(p-tolyl)furan-3-carboxylate (6g). Yellow solid (40%, 82mg), **IR** (neat) ν 2947, 1713, 1594, 1488, 1223, 1090 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 1.46 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 3.88 (s, 3H), 4.40 (t, *J* = 7.2 Hz, 2H), 7.07 (s, 1H), 7.26 – 7.33 (m, 3H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.50 (td, *J* = 1.1 and 7.7 Hz, 1H), 7.84 (dd, J = 1.8 and 8.5 Hz, 1H), 8.00 – 8.05 (m, 2H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 1.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 13.8, 21.5, 37.6, 51.6, 105.9, 108.8, 115.0, 116.2, 119.3, 120.7, 121.2, 122.3, 123.0, 123.3, 126.1, 127.3, 128.3, 129.0, 139.4, 139.8, 140.5, 153.6, 156.3, 164.4. **HRESIMS** calcd. for $C_{27}H_{23}NNaO_3$ ($M+Na^+$): 432.1576; found 432.1579.

Methyl 4-bromo-2-(4-methoxyphenyl)-5-(p-tolyl)furan-3-carboxylate (6Br-a). White solid (92%, 92mg), **Mp:** 131 – 132 °C, **IR** (neat) ν 2953, 1710, 1609, 1495, 1230, 1119, 1034, 836 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.95 – 7.01 (m, 2H), 7.23 – 7.30 (m, 2H), 7.73 – 7.78 (m, 2H), 7.88 - 7.94 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.5, 51.9, 55.5, 96.6, 113.8, 114.8, 122.0, 126.2, 126.4, 129.3, 129.7, 138.7, 148.8, 155.6, 160.7, 163.6. **HRESIMS** calcd. for $C_{20}H_{17}BrNaO_4$

($M+Na^+$): 425.0187; found 425.0183.

Methyl 4-bromo-5-(4-fluorophenyl)-2-(4-methoxyphenyl)furan-3-carboxylate (6Br-b). White solid (87%, 88mg), **Mp:** 161 – 162 °C, **IR** (neat) ν 2958, 1713, 1606, 1494, 1220, 1117, 1032, 836 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 6.95 – 7.01 (m, 2H), 7.12 – 7.19 (m, 2H), 7.72 – 7.77 (m, 2H), 7.98 – 8.03 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 52.0, 55.5, 97.1, 114.0, 115.0, 115.8 (d, *J* = 21.8 Hz), 121.9, 125.5 (d, *J* = 3.3 Hz), 128.4 (d, *J* = 8.2 Hz), 129.9, 147.9, 156.1, 161.1, 162.9 (d, *J* = 248.8 Hz), 163.6. **HRESIMS** calcd. for $C_{19}H_{14}BrFNaO_4$ ($M+Na^+$): 426.9957; found 426.9954.

Methyl 4-bromo-5-(4-chlorophenyl)-2-(p-tolyl)furan-3-carboxylate (6Br-c). White solid (73%, 74mg), **Mp:** 138 – 139 °C, **IR** (neat) ν 2956, 1714, 1585, 1502, 1235, 1118, 1035, 816 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.88 (s, 3H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.41 – 7.45 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.96 – 8.00 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.6, 52.1, 97.8, 115.9, 126.5, 127.5, 127.7, 128.1, 129.0, 129.3, 134.7, 140.4, 147.9, 156.2, 163.5. **HRESIMS** calcd. for $C_{19}H_{14}BrClNaO_3$ ($M+Na^+$): 426.9713; found 426.9708.

Methyl 4-bromo-5-(4-methoxyphenyl)-2-phenylfuran-3-carboxylate (6Br-d). White solid (92%, 89mg), **Mp:** 99 – 100 °C, **IR** (neat) ν 2949, 1706, 1567, 1486, 1026 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 3.88 (s, 3H), 6.93 – 7.05 (m, 2H), 7.36 – 7.52 (m, 3H), 7.71 – 7.86 (m, 2H), 7.88 – 8.06 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.9, 55.3, 95.7, 114.0, 116.0, 121.7, 127.9, 127.9, 128.4, 129.4, 129.5, 149.3, 154.8, 160.0, 163.5. **HRESIMS** calcd. for $C_{19}H_{16}BrO_4$ ($M+H^+$): 387.0232; found 387.0234.

Methyl 5-(4-methoxyphenyl)-2-phenyl-4,5-dihydrothiophene-3-carboxylate 3d-S. Dihydrofuran (**3d**, 0.25 mmol, 1 equiv.) and Lawesson reagent (0.55 equiv.) and dry-toluene were added to a dram vial equipped with a stir bar and a screw cap and the resulting mixture was stirred at 110 °C for 20 h. After this time, the contents of the flask were concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the dihydrothiophene **3d-S** (yellow oil (75%, 61mg))**. IR** (neat) ν 2947, 1707, 1511, 1249 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.49 (dd, *J* = 8.1 and 16.3 Hz, 1H), 3.57 (s, 3H), 3.70 (dd, *J* = 9.4 and 16.3 Hz, 1H), 3.81 (s, 3H), 4.93 (dd, *J* = 8.2 and 9.3 Hz, 1H), 6.86 – 6.93 (m, 2H), 7.34 – 7.47 (m, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 46.7, 51.0, 51.3, 55.5, 114.3, 118.7, 128.1, 128.4, 128.8, 129.3, 133.9, 134.0, 156.9, 159.4, 164.1. **HRESIMS** calcd. for $C_{19}H_{19}O_3S$ ($M+H^+$): 327.1055; found 327.1062.

Methyl 5-(4-methoxyphenyl)-2-phenylthiophene-3-carboxylate (7). The dihydrothiophene **3d-S** (0.25 mmol, 1 equiv) dissolved in toluene was taken into a dram vial equipped with a stir bar and a screw cap. DDQ (0.60 mmol) was added and the

reaction mixture was stirred at 110 °C for 12 h. After this time, the contents of the flask were concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **7** (white solid (51%, 41mg)). **Mp:** 118 – 119 °C, **IR** (neat) ν 2949, 1718, 1608, 1494, 1463, 1252 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 3.85 (s, 3H), 6.92 – 6.96 (m, 2H), 7.39 – 7.44 (m, 3H), 7.52 – 7.57 (m, 4H), 7.60 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 51.6, 55.4, 114.5, 124.4, 126.2, 127.1, 128.1, 128.3, 128.7, 129.8, 133.4, 142.7, 149.2, 159.7, 163.9. **HRESIMS** calcd. for $C_{19}H_{16}NaO_3S$ ($M+Na^+$): 347.0718; found 347.0711.

Methyl 4-bromo-5-(4-methoxyphenyl)-2-phenylthiophene-3-carboxylate (7Br). 7 (0.25 mmol, 1 equiv.) and NBS (1.05 equiv.) and CH_3CN were added to a dram vial equipped with a stir bar and a screw cap and the resulting mixture was stirred at 50 °C for 12 h. After this time, the contents of the flask were concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the bromide **7Br** (white solid (95%, 95mg)). **IR** (neat) ν 2948, 1718, 1604, 1456, 1437, 1249, 1031 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 3.87 (s, 3H), 6.97 – 7.02 (m, 2H), 7.38 – 7.49 (m, 5H), 7.55 – 7.61 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 52.5, 55.4, 106.5, 114.1, 124.5, 128.2, 128.8, 128.9, 130.7, 130.9, 132.6, 138.7, 144.1, 160.0, 165.0. **HRESIMS** calcd. for $C_{19}H_{15}BrNaO_3S$ ($M+Na^+$): 424.9823; found 424.9829.

Methyl 5-(4-methoxyphenyl)-2-phenyl-4-(p-tolyl)thiophene-3-carboxylate (8). $PdCl_2$(dppf) (5 mol%), bromide **7Br** (0.25 mmol, 1 equiv.), and *p*-methylphenylboronic acid (2 equiv.) were added under air to a dram vial equipped with a stir bar and a screw cap. DMF and 2M Na_2CO_3 aq. (2 mL/mmol, 4 equiv.) were added to the mixture under nitrogen atmosphere (charged by general N_2 (99.95%) gas flow) and the reaction mixture was stirred at 80 °C for 12 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc and GPC (Gel Permeation Chromatography) to afford the product **8** (white solid (81%, 84mg)). **Mp:** 174 – 175 °C, **IR** (neat) ν 2953, 1720, 1603, 1457, 1422 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 3.53 (s, 3H), 3.78 (s, 3H), 6.74 – 6.79 (m, 2H), 7.08 – 7.16 (m, 6H), 7.34 – 7.44 (m, 3H), 7.50 – 7.55 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.4, 52.1, 55.3, 114.0, 126.0, 128.5, 128.7, 128.8, 129.1, 129.8, 130.5, 131.8, 132.7, 133.5, 137.1, 137.6, 139.4, 143.1, 159.3, 166.7. **HRESIMS** calcd. for $C_{26}H_{23}O_3S$ ($M+H^+$): 415.1368; found 415.1366.

5-(4-Methoxyphenyl)-2-phenyl-4-(*p*-tolyl)thiophene-3-carboxylic acid 8OH. Ester **8** (0.25 mmol, 1 equiv.) in 0.5 M NaOH aq. (2 eqiv. 4 mL/mmol) and 1,4-dioxane was

stirred at 100 °C for 12 hr. At this time, the mixture was acidified by conc. HCl aq. and extracted with EtOAc to afford the carboxylic acid **8OH** (white solid (95%, 95mg)), **Mp:** 243 – 244 °C, **IR** (neat) ν 2924, 1684, 1603, 1460, 1435 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 3.77 (s, 3H), 6.74 – 6.78 (m, 2H), 7.08 – 7.16 (m, 6H), 7.37 – 7.43 (m, 3H), 7.53 – 7.57 (m, sH). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 21.4, 55.3, 114.0, 125.9, 128.7, 128.8, 129.0, 129.2, 129.9, 130.2, 130.6, 132.5, 133.3, 137.2, 137.8, 139.7, 145.1, 159.3, 169.3. **HRESIMS** calcd. for $C_{25}H_{20}NaO_3S$ ($M+Na^+$): 423.1031; found 423.1041.

2-(4-Methoxyphenyl)-5-phenyl-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene (9). $PdCl_2$(dppf) (10 mol%), carboxylic acid **8OH** (0.25 mmol, 1 equiv.), 1-iodo-4-(trifluoromethyl)benzene (2 equiv.), Cs_2CO_3 (3 equiv.) MS4A (300 mg/mmol) were added under air to a dram vial equipped with a stir bar and a screw cap. Mesitylene was added to the mixture under nitrogen atmosphere (charged by general N_2 (99.95%) gas flow) and the reaction mixture was stirred at 170 °C for 12 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc and GPC (Gel Permeation Chromatography) to afford the product **9** (white solid (70%, 84mg)), **IR** (neat) ν 2956, 1605, 1485, 1454, 1327, 1120 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 3.79 (s, 3H), 6.75 – 6.79 (m, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 7.14 – 7.20 (m, 4H), 7.21 – 7.25 (m, 3H), 7.36 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 21.3, 55.3, 114.0, 124.5 (q, *J* = 271.1 Hz), 124.9 (q, *J* = 3.8 Hz), 126.7, 127.6, 128.7, 128.7 (d, *J* = 32.6 Hz), 129.0, 129.5, 130.5, 130.8, 131.4, 133.2, 134.1, 136.6, 138.0, 138.6, 138.8, 139.0, 140.7, 159.1. **HRESIMS** calcd. for $C_{31}H_{23}F_3NaOS$ ($M+Na^+$): 523.1319; found 523.1311.

ASSOCIATED CONTENT

Supporting Information

Optimization studies for the couplings and spectroscopic data for all new compounds are available free of charge via the Internet at http://pubs.acs.org.

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