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Copper-catalyzed highly regioselective 2-aryloxylation of 2,*x*-dihalopyridines

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ABSTRACT

2,*x*-Dihalopyridines reacted with phenols catalyzed by CuI/TMEDA in the presence of Cs_2CO_3 in DMSO at 110 °C under nitrogen atmosphere for 24 h to afford 2-aryloxypyridines in good to high yields except *p*-nitrophenol. To expand this methodology, a vanilloid receptor ligand used in treatments was prepared in good yield. This method has potential utility in the synthesis of pharmaceuticals, agrochemicals and even natural products.

1. Introduction

It is well known to all that pyridines are key backbones of pharmaceuticals and natural products.[1–3] Among pyridines, substituted 2-aryloxypyridines are widely used as glucagon receptor antagonists,[4] endothelin antagonists,[5,6] anti-hypercholesteremic, anti-hyperlipoproteinemic and anti-hyperglycemic agents,[7] herbicides[8,9] and vanilloid receptor ligands used in treatments[10] (see Fig. 1) etc.

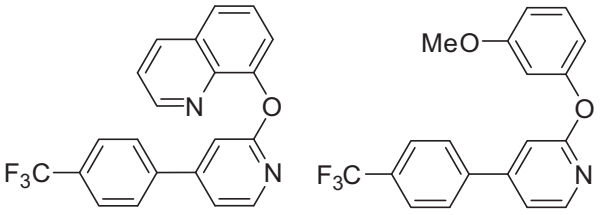
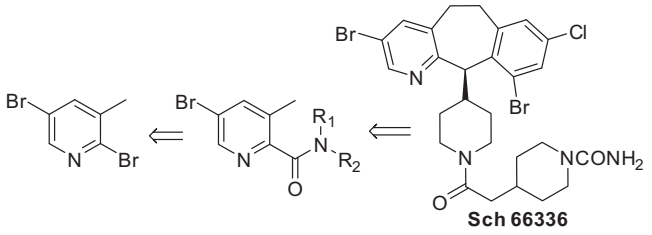


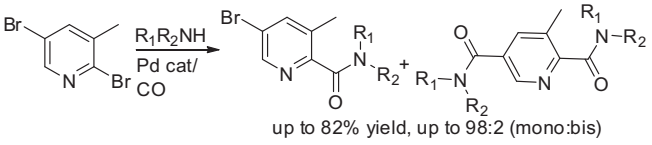
Fig. 1. Structures of two vanilloid receptor ligands.[10]

It had been postulated that the synthesis of **Sch 66336** required an efficient method for the preparation of 3-methyl-5-bromo-2-pyridinecarboxyamides from 2,5-dibromo-3-methyl-pyridine (see Scheme 1).[11]

Wu reported Pd-catalyzed regioselective carbonylation of 2,5-dibromopyridine (see Scheme 2).[11] Bach had reviewed regioselective cross-coupling reactions of multiple halogenated pyridines.[12] Cid reported Pd-catalyzed 2-arylation of 2,4-dibromopyridine via



Scheme 1. Retrosynthetic route for **Sch 66336**.



Scheme 2.

Suzuki reaction but the yields and regioselectivities were not satisfied.[13] The above methods inspired us to develop regioselective C–O coupling of 2,*x*-dihalopyridines and phenols for the synthesis of drugs, agrochemicals, and even natural products.

Recently, Buchwald,[14] Ma,[15] Cristau,[16] Kim,[17] Bao,[18] Xu,[19] Sekar,[20] Sreedhar,[21] Punniyamurthy,[22] Maiti[23] and Hsieh[24] et al. developed efficient Ullman-type intermolecular C–O coupling from aryl halides and phenols. Recently, copper catalyzed cross coupling of aryl halides with phenols were reviewed.[25] Ding reported that 2-bromopyridine reacted with phenol catalyzed by CuBr/(2-pyridyl)acetone to afford 2-phenoxypyridine in 98% yield.[26]

To the best of our knowledge, copper-catalyzed regioselective C–O coupling reaction has not been reported before. Herein, we

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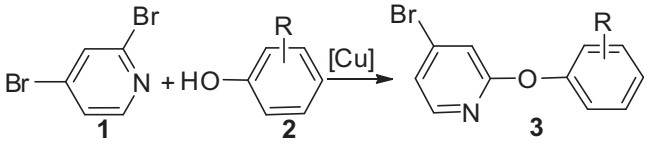
report Cu-catalyzed regioselective aryloxylation of 2,*x*-dihalopydines (see Scheme 3) and expand its utility in organic synthesis.



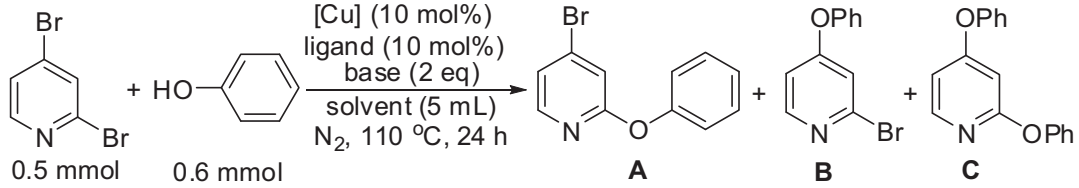
Scheme 3.

2. Results and discussion

As indicated in Table 1, the investigation was initiated by using the coupling of 2,4-dibromopyridine and phenol as a model reaction to explore the optimized reaction conditions.

The scope of the copper-catalyzed regioselective C–O bond formation was explored by using a variety of 2,*x*-dihalopyridines with substituted phenols under the optimized conditions. As shown in Table 2, the listed 2,*x*-pyridines well underwent coupling with all phenols bearing electron donating groups (see entries 1–3, 6–9, 12–15, and 18–19). 2,4-Dibromopyridine, 2,3-dibromopyridine and 2,5-dibromopyridine reacted with *p*-chlorophenol to also give high yields (see entries 4, 10 and 16, Table 2). Phenol bearing nitro group, which is a strong electron withdrawing group gave very low yields (see entries 5, 11 and 17, Table 2). 2,3,5-Trichloropyridine reacted with 4-methylphenol to give product **3s** in 93% yield. 2,3-Dichloro-5-trifluoromethylpyridine (**1e**) bearing trifluoromethyl group, which is a strong electron withdrawing group is unreactive and showed worse selectivity, so the yield of **3t** is very low. The above results indicated that electronic variations on the phenol rings have a significant impact on the yields. Why the regioselectivity is

Table 1
Copper-catalyzed phenoxylation of 2,4-dibromopyridine: optimization of the reaction conditions[a]



Entry	Copper	Ligand	Base	Solvent	Temperature (°C)	**A**: yield[e] (%)	**B**: yield[e] (%)	**C**: yield[e] (%)
1	CuI	L-proline	K_2CO_3	Toluene	110	0	0	0
2	CuI	L-proline	K_2CO_3	Dioxane	110	0	0	0
3	CuI	L-proline	Cs_2CO_3	Toluene	110	0	0	0
4	CuI	L-proline	Cs_2CO_3	Dioxane	110	0	0	0
5	CuI	L-proline	Cs_2CO_3	DMSO	110	45	21	0
6	CuI	1,10-Phenanthroline	Cs_2CO_3	DMSO	110	97	1.8	0
7	CuI	1,10-Phenanthroline	Cs_2CO_3	DME	Reflux	27	10	2.6
8	CuI	1,10-Phenanthroline	Cs_2CO_3	Toluene	110	68	2	0
9	**CuI**	**TMEDA**[b]	**Cs_2CO_3**	**DMSO**	110	**98**	**0**	**0**
10	CuI	PMDETA[c]	Cs_2CO_3	DMSO	110	52	6	1.2
11	CuI	DMEDA[d]	Cs_2CO_3	DMSO	110	43	5	0
12	CuI	TMEDA	K_2CO_3	DMSO	110	79	5.7	1.8
13	CuI	TMEDA	K_3PO_4	DMSO	110	90	1	0
14	CuI	TMEDA	Na_2CO_3	DMSO	110	46	1.2	0
15	CuI	TMEDA	KOAc	DMSO	110	47	0	0
16	CuCl	TMEDA	Cs_2CO_3	DMSO	110	95	0	0
17	Cu_2O	TMEDA	Cs_2CO_3	DMSO	110	94	0	0
18	CuBr	TMEDA	Cs_2CO_3	DMSO	110	95	0	0
19			Cs_2CO_3	DMSO	110	54	0	0

Bold represents the best reaction condition.
[a] Reaction conditions: CuI (0.05 mmol), ligand (0.05 mmol), 2,4-dibromopyridine (0.5 mmol), phenol (0.6 mmol), bases (1.0 mmol), solvents (5.0 mL), 110 °C, N_2, 24 h.
[b] TMEDA (tetramethylethylenediamine).
[c] PMDETA (1,1,4,7,7-pentamethyldiethylenetriamine).
[d] DMEDA (*N*,*N*′-dimethylethylenediamine).
[e] Isolated yield.

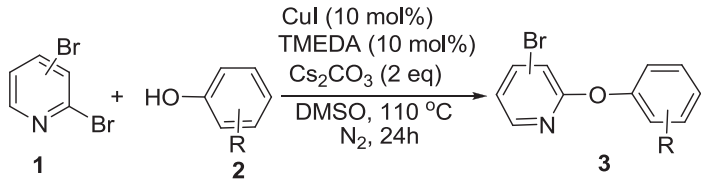
It was found that, under the catalysis of CuI and L-proline, 2,4-dibromopyridine in DMSO was not consumed completely after 24 h at 110 °C, delivering **A** in 45% yield and **B** in 21% yield (entry 5, Table 1). Replacement of L-proline with PMEDTA or DMEDA, gave improved regioselectivity (entries 10 and 11). Replacement of L-proline with 1,10-phenanthroline or TMEDA gave high regioselectivity and high yield (entries 6 and 9). Changing bases from CS_2CO_3 to K_3PO_4, K_2CO_3, Na_2CO_3, or KOAc also decreased the reaction yields (entries 12–15). When CuCl, Cu_2O or CuBr were used instead of CuI, the reaction yields only decreased slightly (entries 16–18). In absence of copper and ligand, 2,4-dibromopyridine reacted with phenol to afford the product in only 54% yield (entry 19). Based on these results, we concluded that, with CuI/TMEDA as the catalyst, Cs_2CO_3 as the base, and DMSO as the solvent, this was the optimized set of conditions for this transformation (see entry 9, Table 1).

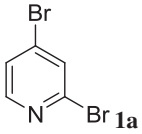
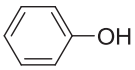
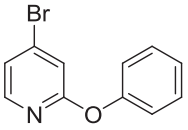
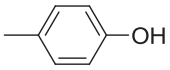
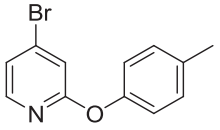
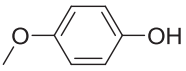
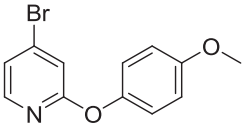
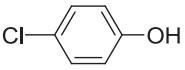
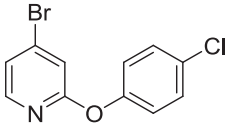
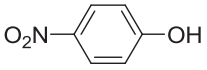
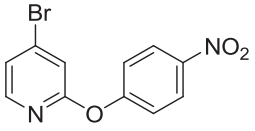
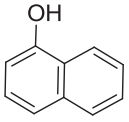
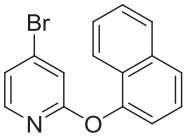
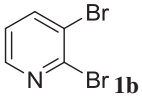
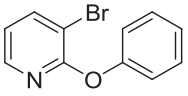
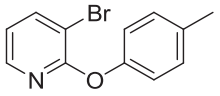
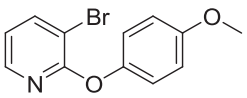
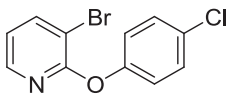
so high for the aryloxylation of 2,4-dibromopyridine, 2,5-dibromopyridine, and 2,3-dibromopyridine? We can explain that the 2-bromo of 2,*x*-dibromopyridine is more reactive than the 4-bromo, 5-bromo, and 3-bromo of 2,*x*-dibromopyridine.[13]

After completion of the reaction, to demonstrate the applicability of this method in the synthesis of drugs, agrochemicals and even natural products, we functionalized **3a** through Suzuki coupling in 98% yield and through Sonogashira coupling in 93% yield (Scheme 4).

To expand this methodology, a vanilloid receptor ligand[10] used in treatments (compound **7**) was prepared (see Scheme 5). 2,4-Dibromopyridine reacted with 8-hydroxyquinoline with the standard method to give compound **6** in 71% yield. Compound **6** reacted with 4-trifluoromethylphenyl boronic acid in the presence of $Pd(OAc)_2/PPh_3$ with KOH in MeOH to afford compound **7** in 74% yield. Trifluoromethyl in 4-trifluoromethylphenyl boronic

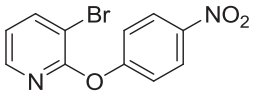
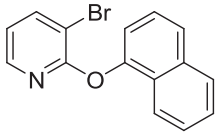
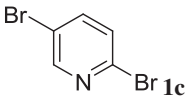
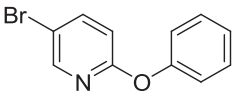
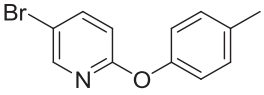
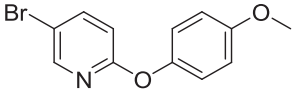
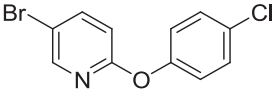
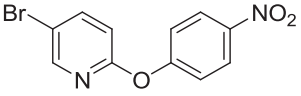
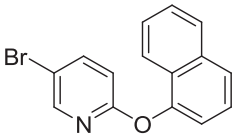
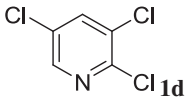
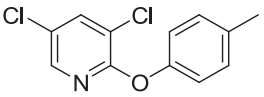
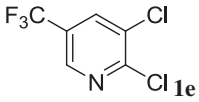
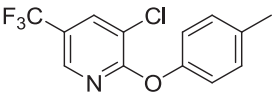
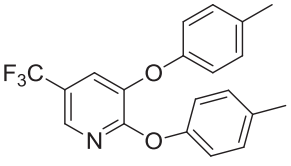
Table 2
Synthesis of various 2-aryloxypyridines from 2,*x*-dihalopyridines and substituted phenols



Entry	2,*x*-Dibromopyridines	Phenols	Product	Yield (%)
1	 **1a**	 **2a**	 **3a**	91
2	**1a**	 **2b**	 **3b**	89
3	**1a**	 **2c**	 **3c**	91
4	**1a**	 **2d**	 **3d**	86
5	**1a**	 **2e**	 **3e**	7
6	**1a**	 **2f**	 **3f**	83
7	 **1b**	**2a**	 **3g**	91
8	**1b**	**2b**	 **3h**	98
9	**1b**	**2c**	 **3i**	75
10	**1b**	**2d**	 **3j**	90

(*continued on next page*)

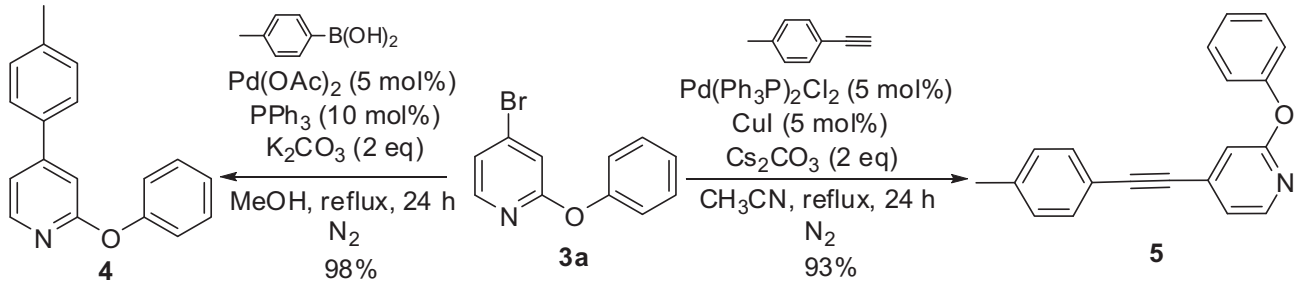
Table 2 (*continued*)

Entry	2,*x*-Dibromopyridines	Phenols	Product	Yield (%)
11	**1b**	**2e**	 **3k**	18
12	**1b**	**2f**	 **3l**	77
13	 **1c**	**2a**	 **3m**	96
14	**1c**	**2b**	 **3n**	91
15	**1c**	**2c**	 **3o**	95
16	**1c**	**2d**	 **3p**	92
17	**1c**	**2e**	 **3q**	7
18	**1c**	**2f**	 **3r**	85
19	 **1d**	**2b**	 **3s**	93
20	 **1e**	**2b**	 **3t**	24
			 **3u**	10

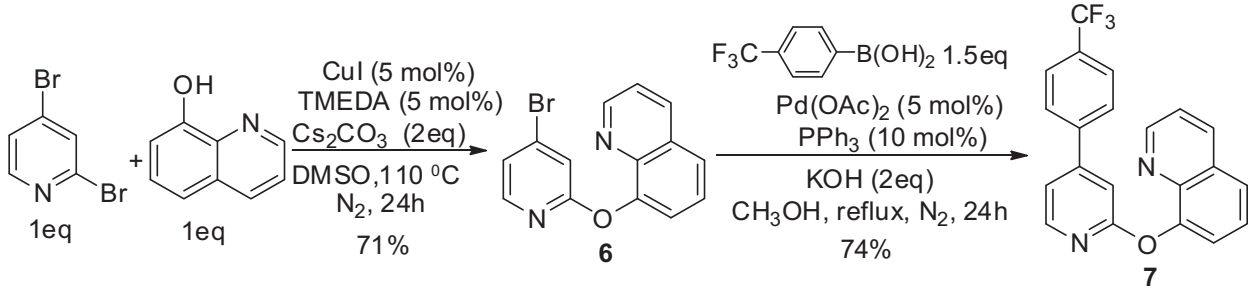
acid is a strong electron withdrawing group, so the yield of compound **7** is lower than that of compound **4**. Therefore, a Cu-catalyzed regioselective aryloxylation of 2,*x*-dihalopyridines would be an interesting approach to some drugs and even natural products.

3. Conclusions

In conclusion, we have developed a facile and efficient approach for highly regioselective aryloxylation of 2,*x*-dihalopyridines with up to 96% yield. The CuI/TMEDA catalytic system displays excellent



Scheme 4.



Scheme 5.

functional group compatibility and high regioselectivity in the presence of a broad range of functional groups though *p*-nitrophenol gave low yields. High regioselectivity and high yield is owing to the different electro property of 2- and other halogen in the 2,*x*-dihalopyridines. To expand this methodology, 4-bromo-2-phenoxypyridine was functionalized with Suzuki and Sonogashira reaction in high yield. We also prepared a vanilloid receptor ligand in good yield with Suzuki reaction. This method has utility in the synthesis of pharmaceuticals, agrochemicals, and even natural products. High regioselective fuctionalization of 2,*x*-dibromopyridines is currently underway.

4. Experimental

4.1. General procedure for the copper-catalyzed coupling reaction of 2,*x*-dihalopyridines and phenols

2,4-Dibromopyridine (0.236 g, 1 mmol) and phenol (0.094 g, 1 mmol), CuI (19.0 mg, 0.1 mmol), TMEDA (11.6 mg, 0.1 mmol), and cesium carbonate (0.65 g, 2 mmol) were placed in DMSO (5 mL). The reaction was stirred at 110 °C under nitrogen atmosphere for 24 h. When the reaction mixture was cooled, the reaction mixture was filtered. The mixture was dissolved with dichloromethane (25 mL). Then the mixture was washed with brine (3×30 mL). The organic phase was dried over sodium sulfate. After evaporation of the solvent, the mixture was subjected to column chromatography with petroleum ether/ethyl acetate (20:1) as eluent to give pure product.

*4.1.1. Compound **3a**.* Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.20 (d, *J*=7.6 Hz, 1H), 7.45 (t, *J*=7.6 Hz, 2H), 7.29 (t, *J*=7.2 Hz, 1H), 7.09 (d, *J*=7.6 Hz, 2H), 6.98 (d, *J*=2.0 Hz, 1H), 6.82 (dd, J_1=2.4 Hz, J_2=2.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.3, 153.7, 151.2, 143.1, 130.7, 126.3, 121.1, 115.9, 112.1; MS (ESI): 249.9 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_9BrNO$: 249.9852, found: 249.9862.

*4.1.2. Compound **B**.* Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.00 (d, *J*=5.2 Hz, 1H), 7.40 (t, *J*=8.0 Hz, 2H), 7.21 (t, *J*=7.6 Hz, 1H), 7.08–7.13 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.6, 153.8, 148.5, 134.9, 130.0, 125.4, 122.1, 121.5, 114.9; MS (EI): 248.0 (M^+); HRMS (EI) calcd for $C_{11}H_8BrNO$: 248.9789, found: 248.9793.

*4.1.3. Compound **C**.* White solid, mp 87–88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.04 (d, *J*=5.6 Hz, 1H), 7.36–7.43 (m, 4H), 7.10–7.26 (m, 6H), 6.58 (dd, J_1=2.0 Hz, J_2=2.4 Hz, 1H), 6.39 (t, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 167.9, 165.8, 154.3, 149.1, 130.5, 129.9, 125.8, 125.0, 121.5, 121.2, 108.4, 99.0; MS (EI): 262.0 (M^+); HRMS (EI) calcd for $C_{17}H_{13}NO_2$: 263.0946, found: 263.0944.

*4.1.4. Compound **3b**.* Yellow solid, mp 63.1–64.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.17 (d, *J*=5.6 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 2H), 6.96 (d, *J*=8.4 Hz, 3H), 6.80 (dd, J_1=2.4 Hz, J_2=2.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.5, 151.3, 151.2, 143.2, 136.0, 131.1, 120.8, 115.7, 111.9, 21.1; MS (ESI): 263.9 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{12}H_{11}BrNO$: 264.0019, found: 264.0016.

*4.1.5. Compound **3c**.* Yellow solid, mp 64.7–66.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.18 (d, *J*=6.0 Hz, 1H), 6.94–7.03 (m, 5H), 6.79 (dd, J_1=2.8 Hz, J_2=2.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.9, 157.7, 151.1, 146.8, 143.1, 122.1, 115.6, 115.4, 111.7, 55.9; MS (ESI): 280.0 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{12}H_{11}BrNO_2$: 279.9968, found: 279.9955.

*4.1.6. Compound **3d**.* Pale yellow solid, mp 67.4–68.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.22 (d, *J*=6.0 Hz, 1H), 7.39–7.43 (m, 2H), 6.98–7.06 (m, 3H), 6.82 (dd, J_1=2.4 Hz, J_2=2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.9, 152.2, 151.4, 143.2, 131.6, 130.7, 122.4, 115.9, 112.0; MS (ESI): 283.9 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_8BrClNO$: 283.9472, found: 283.9460.

*4.1.7. Compound **3e**.* Yellow solid, mp 121.9–123.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.27–8.29 (m, 2H), 8.03 (d, *J*=5.6 Hz, 1H), 7.24–7.29 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.0, 159.1, 148.3, 144.7, 135.5, 125.8, 123.6, 121.5, 116.1; MS (EI): 295.0 (M^+); HRMS (EI) calcd for $C_{11}H_7BrN_2O_3$: 293.9640, found: 293.9637.

*4.1.8. Compound **3f**.* Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.17 (d, *J*=6.0 Hz, 1H), 7.77–7.91 (m, 3H), 7.45–7.55 (m, 3H), 8.17

(d, J=7.6 Hz, 1H), 6.99 (d, J=2.0 Hz, 1H), 6.80 (dd, J_1=2.0 Hz, J_2=2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.7, 151.3, 149.3, 143.3, 135.3, 128.4, 127.2, 127.1, 126.8, 126.5, 126.0, 121.5, 117.2, 115.7, 111.7; MS (ESI): 302.0 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{11}BrNO$: 300.0019, found: 300.0022.

4.1.9. Compound ***3g***. Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.05 (dd, J_1=2.0 Hz, J_2=2.0 Hz, 1H), 7.90 (dd, J_1=1.6 Hz, J_2=2.0 Hz, 1H), 7.40 (t, J=8.0 Hz, 2H), 7.22 (t, J=7.2 Hz, 1H), 7.15 (d, J=8.0 Hz 2H), 6.86 (q, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.1, 153.9, 146.2, 142.8, 129.8, 125.3, 121.6, 119.8, 108.0; MS (ESI): 249.9 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_9BrNO$: 249.9862, found: 249.9861.

4.1.10. Compound ***3h***. Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.04 (dd, J_1=1.6 Hz, J_2=1.6 Hz, 1H), 7.89 (dd, J_1=1.2 Hz, J_2=1.6 Hz, 1H), 7.19 (d, J=5.2 Hz, 2H), 7.03 (d, J=8.4 Hz, 2H), 6.84 (dd, J_1=4.4 Hz, J_2=4.8 Hz 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.3, 151.6, 146.2, 142.7, 134.9, 130.4, 121.5, 119.5, 107.8, 21.2; MS (EI): 264.0 (M^+); HRMS (EI) calcd for $C_{12}H_{10}BrNO$: 262.9946, found: 262.9950.

4.1.11. Compound ***3i***. White solid, mp 86.6–87.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.05 (dd, J_1=0.8 Hz, J_2=0.8 Hz, 1H), 7.90 (d, J=7.6 Hz, 1H); 7.09 (d, J=8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 6.85 (dd, J_1=5.2 Hz, J_2=4.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.5, 157.1, 147.3, 146.2, 142.8, 122.8, 119.5, 114.9, 107.7, 55.9; MS (ESI): 280.0 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{12}H_{11}BrNO_2$: 279.9968, found: 279.9967.

4.1.12. Compound ***3j***. Pale yellow solid, mp 58.6–60.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.05 (dd, J_1=1.2 Hz, J_2=1.2 Hz, 1H), 7.92 (dd, J_1=1.6 Hz, J_2=1.6 Hz, 1H), 7.36 (d, J=10.0 Hz, 2H), 7.10 (d, J=8.8 Hz, 2H), 6.89 (dd, J_1=4.8 Hz, J_2=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 159.8, 152.4, 146.1, 143.0, 130.6, 129.8, 123.1, 120.1, 107.9; MS (EI): 285.0 (M^+); HRMS (EI) calcd for $C_{11}H_6BrClNO$: 281.9321, found: 281.9325.

4.1.13. Compound ***3k***. Pale yellow solid, mp 100.4–101.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.29 (d, J=8.8 Hz, 2H), 8.12 (dd, J_1=1.6 Hz, J_2=1.6 Hz, 1H), 8.00 (dd, J_1=1.2 Hz, J_2=1.2 Hz, 1H), 7.29–7.31 (m, 2H), 7.02 (q, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 159.2, 158.9, 146.3, 144.8, 143.5, 125.8, 121.6, 121.3, 108.6; MS (EI): 294.0 (M^+); HRMS (EI) calcd for $C_{11}H_7BrN_2O_3$: 293.9640, found: 293.9638.

4.1.14. Compound ***3l***. Yellow solid, mp 86.6–87.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.92–7.96 (m, 3H), 7.86 (d, J=7.6 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.42–7.49 (m, 3H), 7.28 (d, J=7.6 Hz, 1H), 6.83 (q, J=4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.4, 149.9, 146.4, 142.9, 135.2, 128.2, 127.6, 126.6, 126.5, 125.8, 125.6, 122.1, 119.9, 117.8, 107.7; MS (ESI): 324.0 $(M+H+Na)^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{11}BrNO$: 300.0019, found: 300.0021.

4.1.15. Compound ***3m***. Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.21 (d, J=2.4 Hz, 1H), 7.74 (dd, J_1=2.4 Hz, J_2=3.2 Hz, 1H), 7.39 (t, J=8.0 Hz, 2H), 7.22 (t, J=5.6 Hz, 1H), 7.11 (d, J=8.0 Hz, 2H), 6.81 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.8, 154.0, 148.6, 142.2, 130.0, 125.3, 121.4, 113.7, 113.3; MS (EI): 250.0 (M^+); HRMS (EI) calcd for $C_{11}H_8BrNO$: 248.9789, found: 248.9785.

4.1.16. Compound ***3n***. Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.20 (d, J=1.6 Hz, 1H), 7.72 (dd, J_1=2.8 Hz, J_2=2.0 Hz, 1H); 7.19 (d, J=8.0 Hz, 2H), 6.99–7.01 (m, 2H), 6.79 (d, J=8.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.1, 151.6, 148.5, 142.1, 134.9, 130.5, 121.3, 113.4, 113.1, 21.1; MS (ESI): 264.1 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{12}H_{11}BrNO$: 264.0013, found: 264.0019.

4.1.17. Compound ***3o***. Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.20 (d, J=2.4 Hz, 1H), 7.72 (dd, J_1=2.4 Hz, J_2=2.8 Hz, 1H), 7.02–7.06 (m, 2H), 6.89–6.93 (m, 2H), 6.78 (d, J=8.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.2, 157.0, 148.5, 147.2, 142.1, 122.5, 115.0, 113.3, 112.9, 55.8; MS (EI): 279.0 (M^+); HRMS (EI) calcd for $C_{12}H_9BrNO_2$: 277.9817, found: 277.9820.

4.1.18. Compound ***3p***. Pale yellow solid, mp 40.3–41.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.20 (d, J=2.4 Hz, 1H), 7.77 (dd, J_1=2.4 Hz, J_2=2.8 Hz, 1H), 7.31 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 6.85 (d, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.4, 152.5, 148.6, 142.4, 130.5, 130.0, 122.8, 114.1, 113.5; MS (ESI): 283.8 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_8BrClNO$: 283.9468, found: 283.9472.

4.1.19. Compound ***3q***. Yellow solid, mp 87.6–89.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.24–8.29 (m, 3H), 7.87 (dd, J_1=2.4 Hz, J_2=2.4 Hz, 1H), 7.27 (d, J=8.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.2, 159.3, 148.7, 144.5, 142.9, 125.8, 121.2, 115.4, 114.4; MS (EI): 294.0 (M^+); HRMS (EI) calcd for $C_{11}H_7BrN_2O_3$: 293.9640, found: 293.9643.

4.1.20. Compound ***3r***. Pale yellow solid, mp 83.3–84.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.18 (d, J=2.4 Hz, 1H), 7.90 (dd, J_1=8.4 Hz, J_2=8.0 Hz, 2H), 7.72–7.75 (m, 2H), 7.42–7.51 (m, 3H), 7.21 (d, J=8.0 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.4, 149.9, 148.9, 142.3, 135.2, 128.3, 127.6, 126.8, 126.6, 126.0, 125.7, 122.1, 117.5, 113.8, 112.7; MS (EI): 298.1 (M^+); HRMS (EI) calcd for $C_{15}H_9BrNO$: 297.9868, found: 297.9867.

4.1.21. Compound ***3s***. Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.95 (d, J=2.0 Hz, 1H), 7.72 (d, J=2.0 Hz, 1H), 7.20 (d, J=8.4 Hz, 2H), 7.02 (dt, J_1=2.4 Hz, J_2=2.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 158.1, 151.2, 143.7, 138.9, 135.2, 130.4, 125.5, 121.4, 119.6, 21.1; MS (EI): 252.1 (M^+); HRMS (EI) calcd for $C_{12}H_9Cl_2NO$: 253.0061, found: 253.0060.

4.1.22. Compound ***3t***. Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.26 (s, 1H), 7.96 (d, J=2.0 Hz, 1H), 7.24 (d, J=8.4 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.8, 150.8, 142.9 (q, J=4.3 Hz), 136.5 (d, J=2.7 Hz), 135.8, 130.6, 124.5, 122.2 (m), 121.6, 119.5, 21.2; MS (EI): 287.1 (M^+); HRMS (EI) calcd for $C_{13}H_9ClF_3NO$: 287.0325, found: 287.0324.

4.1.23. Compound ***3u***. Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.10 (s, 1H), 7.35 (d, J=1.6 Hz, 1H), 7.20 (d, J=6.4 Hz, 4H), 7.02 (dd, J_1=8.4 Hz, J_2=8.0 Hz, 4H), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.9, 153.5, 151.0, 139.0 (d, J=724.2 Hz), 138.0 (q, J=5.0 Hz), 134.7, 130.9, 130.4, 124.9, 122.8, 122.2 (d, J=8.0 Hz), 121.9, 121.7, 119.2, 21.1, 21.0; MS (EI): 359.0 (M^+); HRMS (EI) calcd for $C_{20}H_{16}F_3NO_2$: 359.1133, found: 359.1129.

4.1.24. Compound ***4***. Brown liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.50 (d, J=5.2 Hz, 1H), 7.81 (d, J=8.4 Hz, 2H), 7.40 (t, J=8.0 Hz, 2H), 7.21–7.26 (m, 4H), 7.11 (d, J=8.0 Hz, 2H), 6.73 (dd, J_1=2.4 Hz, J_2=2.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.8, 159.8, 154.5, 151.2, 139.4, 136.4, 130.4, 129.6, 127.0, 125.5, 120.9, 110.6, 109.0, 21.5; MS (ESI): 262.1 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{16}NO$: 262.1226, found: 262.1223.

4.1.25. Compound ***5***. Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.43 (d, J=5.6 Hz, 1H), 7.44 (dd, J_1=8.0 Hz, J_2=7.6 Hz, 4H), 7.24–7.28 (m, 1H), 7.11 (dd, J_1=8.0 Hz, J_2=7.6 Hz, 4H), 7.02 (d, J=2.4 Hz, 1H), 6.79 (dd, J_1=2.0 Hz, J_2=2.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.1, 154.0, 151.5, 145.2, 139.5, 132.2, 130.5, 129.3, 125.8, 121.0, 119.1, 115.2, 111.7, 90.1, 88.0, 21.7; MS (ESI): 286.0 $[M+H]^+$; HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{16}NO$: 286.1226, found: 286.1222.

4.1.26. Compound ***6***. Yellow solid, mp 91–92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.99–8.89 (m, 1H), 8.17–8.25 (m, 2H), 7.79 (dd,

J_1=2.4 Hz, J_2=2.4 Hz, 1H), 7.56–7.51 (m, 1H), 7.45–7.48 (m, 2H), 6.96 (s, 1H), 6.81–6.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.8, 151.1 (d, J=4.2 Hz), 149.5, 143.1, 141.4, 136.5, 130.3, 126.9, 126.4, 122.4, 121.1, 115.9, 112.0; MS (EI): 301.0 (M^+); HRMS (EI) calcd for $C_{14}H_9BrN_2O$: 299.9898, found: 299.9893.

4.1.27. Compound **7**. White solid, mp 129–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.91 (dd, J_1=1.6 Hz, J_2=1.6 Hz, 1H), 8.53 (d, J=5.2 Hz, 1H), 8.24 (dd, J_1=1.6 Hz, J_2=1.6 Hz, 1H), 8.02 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.4 Hz, 1H), 7.67 (d, J=8.0 Hz, 2H), 7.58 (t, J=8.0 Hz, 1H), 7.42–7.50 (m, 3H), 6.77 (dd, J_1=2.4 Hz, J_2=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.6, 158.1, 151.6, 151.0, 150.3, 142.8, 141.7, 136.5, 131.1 (q, J=32.7 Hz), 130.3, 127.5, 126.9, 125.8 (t, J=5.1 Hz), 124.4 (d, J=811.8 Hz), 123.1, 122.4, 120.7, 111.4, 110.0; MS (EI): 365.0 (M^+); HRMS (EI) calcd for $C_{21}H_{13}F_3N_2O$: 366.0980, found: 366.0981.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.10.025.

References and notes

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