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Chemoselective Suzuki Cross-Coupling Reactions of Chiral Pyrrolizines

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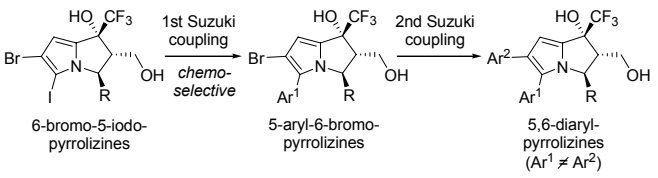
Pyrrolizines have potent cytostatic effects and are thus potentially useful for the development of antitumor and antiviral agents.[1] In particular, chiral trifluoromethylated pyrrolizines would play a unique and significant role in medicinal chemistry because the introduction of a trifluoromethyl group into pharmaceuticals often enhances their physical and/or chemical properties.[2] Recently, we reported that the enantio- and diastereoselective organocatalytic cascade conjugate addition-aldol reactions of a series of 2-trifluoroacetylpyrroles to α,β-unsaturated aldehydes afford highly functionalized chiral pyrrolizines that bear a trifluoromethyl group at the stereogenic center in good yields, high enantioselectivities, and excellent diastereoselectivities.[3] Using the chiral pyrrolizines as the cascade products, we planned the development of an efficient synthesis of unsymmetrically diarylsubstituted chiral pyrrolizines *via* two sequential Suzuki cross-coupling reactions with different arylboronic acids in a highly chemoselective controlled manner.[4] Specifically, in these two sequential Suzuki couplings of multiple halogenated heterocycles,[5] the use of pyrrolizines remains unexplored, in spite of the importance of pyrrolizines as pharmacophores in biologically active compounds. Here, we report the development of the efficient synthetic route of a series of unsymmetrically 5,6-diarylsubstituted chiral pyrrolizines *via* chemoselective Suzuki cross-coupling reactions of chiral 6-bromo-5-iodopyrrolizines, followed by the sequential 2nd Suzuki cross-coupling reaction (Scheme 1).

To explore the feasibility of chemoselective Suzuki cross-coupling reactions of 6-bromo-5-iodopyrrolizines, prepared according to our previous paper,[3] with various arylboronic acids, the Suzuki couplings of 6-bromo-5-iodopyrrolizine **1a** with 3-nitrophenylboronic acid (**2**) were carried out in the presence of $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base in 1,4-dioxane-H_2O solution at elevated temperature (Table 1). The initial cross-couplings attempts using $Pd(PPh_3)_4$ (5 mol %) and K_2CO_3 (200 mol %) in 1,4-dioxane (0.2 M)-H_2O (1.0 M) solution at 60 °C chemoselectively afforded the desired coupling product, 6-bromo-5-(3-nitrophenyl)pyrrolizines **3**, in 44% yield,

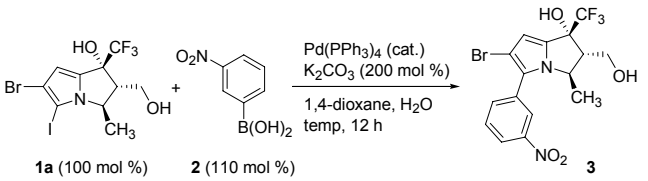


Scheme 1. Synthetic approach to unsymmetrically 5,6-diarylsubstituted chiral pyrrolizines *via* two sequential Suzuki cross-coupling reactions

without 5-iodo-6-(3-nitrophenyl)pyrrolizine as the by-product (Table 1, entry 1). The chemoselective coupling product **3** was identified by ^{1}H NMR and high-resolution mass spectroscopy analyses. At 80 °C, the coupling product **3** showed an increased yield of 57% (Table 1, entry 2). Furthermore, when the loading of $Pd(PPh_3)_4$ was increased to 10 mol %, the coupling product **3** was obtained in 63% yield (Table 1, entry 3). Remarkably, when the concentration of the 1,4-dioxane-H_2O co-solvent was decreased to 0.1 M and 0.15 M, respectively, with the other reaction conditions remaining the same, the cross-coupling reaction afforded the coupling product **3** in 74% yield (Table 1, entry 4). At higher temperatures, under otherwise identical conditions, the coupling product **3** was obtained in a decreased yield of 56% (Table 1, entry 5).

In addition, we applied the optimized conditions of the chemoselective Suzuki cross-coupling reaction of 6-bromo-5-iodopyrrolizine **1a** to the site-selective Suzuki cross-coupling reaction[6] of 5,6-dibromopyrrolizine **4**, generally controlled by electronic and steric parameters, to obtain the desired product, 6-bromo-5-(3-nitrophenyl)pyrrolizines **3**; this product is the same as that obtained from chemoselective couplings (Scheme 2). However, the site-selective cross-coupling reaction afforded the desired coupling product **3** and the symmetrical 5,6-diarylpyrrolizine **5** as the by-product in low selectivity and poor yields. Hence, the chemoselective couplings proved superior in the case of 6-bromo-5-iodopyrrolizine **1a**.

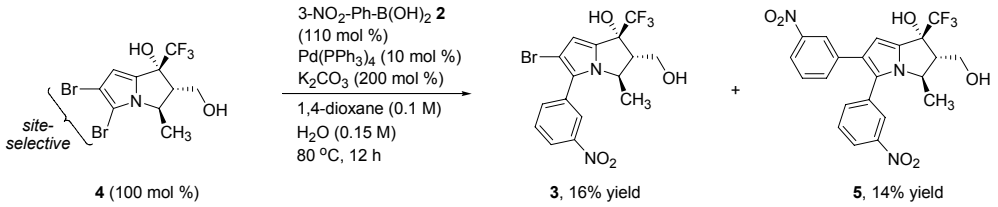
Table 1. Optimization of chemoselective Suzuki cross-coupling reactions of 6-bromo-5-iodopyrrolizine **1a** with 3-nitrophenylboronic acid (**2**)[a]



1a (100 mol %) **2** (110 mol %) **3**

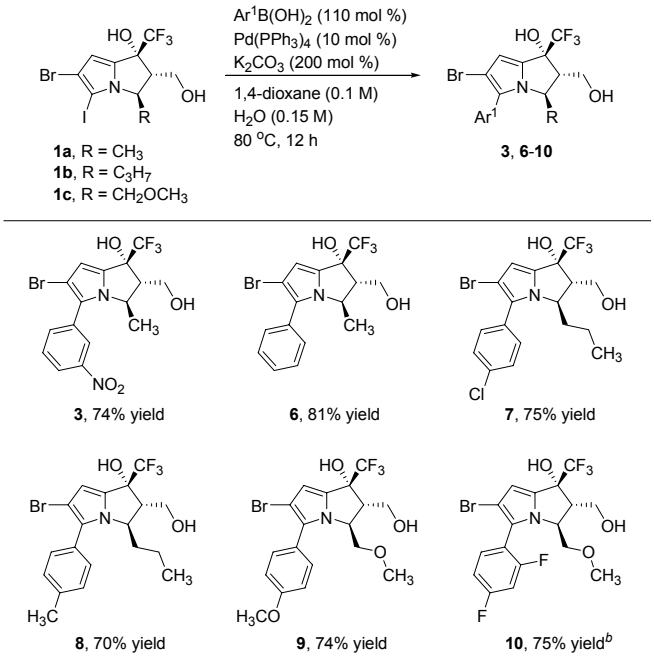
entry	$Pd(PPh_3)_4$ (mol %)	1,4-dioxane (M)	H_2O (M)	temp (°C)	yield (%)
1	5	0.2	1.0	60	44
2	5	0.2	1.0	80	57
3	10	0.2	1.0	80	63
4	**10**	**0.1**	**0.15**	**80**	**74**
5	10	0.1	0.15	100	56

[a]Procedure: To a 1,4-dioxane (0.1 M) of **1a** (100 mol %) was added $Pd(PPh_3)_4$ (10 mol %) at rt. After stirring for 20 min, K_2CO_3 (200 mol %) in H_2O (0.15 M) and arylboronic acid (110 mol %) were added. The mixture was stirred at 60, 80, or 100 °C for 12 h.



Scheme 2. Site-selective Suzuki cross-coupling reaction of 5,6-dibromopyrrolizine **4** with 3-nitrophenylboronic acid (**2**)

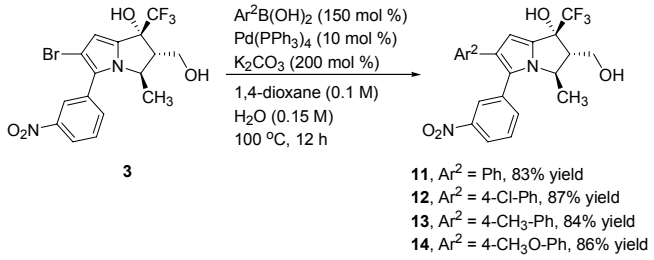
Table 2. Chemoselective Suzuki cross-coupling reactions of 6-bromo-5-iodopyrrolizines **1** with various boronic acids[a]



[a]Procedure: See the Experimental Section. [b]1.5 eq of 2,4-difluorophenylboronic acid was used.

To expand the scope of the chemoselective Suzuki cross-coupling reactions of 6-bromo-5-iodopyrrolizines **1a**-**1c**, which bear aliphatic and methyl-protected hydroxymethyl substituents, the cross-couplings of the same compounds with a series of arylboronic acids having various electron-withdrawing and electron-donating substituents were explored under the optimized reaction conditions (Table 2). The corresponding coupling products **3** and **6**-**10** were chemoselectively obtained in high yields.

Next, we further explored the sequential 2nd Suzuki cross-coupling reactions of chiral 5-aryl-6-bromopyrrolizines with various arylboronic acids to obtain unsymmetrically 5,6-diarylsubstituted chiral pyrrolizines (Scheme 3). As a representative substrate in the 2nd Suzuki cross-coupling reactions, 6-bromo-5-(3-nitrophenyl)pyrrolizines **3** underwent the cross-couplings with a series of arylboronic acids (150 mol %) bearing electron-withdrawing and electron-donating substituents in the presence of $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 (200 mol %) in 1,4-dioxane (0.1 M)-H_2O (0.15 M) solution at 100 °C to provide the desired unsymmetrical 5,6-diarylpyrrolizines **11**-**14** in high yields.



Scheme 3. Synthesis of unsymmetrical diarylpyrrolizines **11**-**14** *via* the sequential 2nd Suzuki couplings of 6-bromo-5-(3-nitrophenyl) pyrrolizines **3** with various arylboronic acids

In summary, the chemoselective Suzuki cross-coupling reaction between chiral 6-bromo-5-iodopyrrolizines and a series of arylboronic acids has been achieved using $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base in 1,4-dioxane-H_2O solution. The cross-coupling reaction provides chemoselectively various chiral 5-aryl-6-bromopyrrolizines in high yields. The sequential 2nd Suzuki cross-coupling reaction of 6-bromo-5-(3-nitrophenyl)pyrrolizines with arylboronic acids bearing electron-withdrawing and electron-donating substituents affords a variety of unsymmetrically 5,6-diarylsubstituted chiral pyrrolizines in high yields. In addition, this is the first example of two sequential Suzuki cross-coupling reactions of dihalopyrrolizines to provide unsymmetrical diarylpyrrolizines. Further studies on the development of two sequential Suzuki cross-coupling reactions are underway.

Experimental Section

General Procedure for the Chemoselective Suzuki Cross-coupling Reactions. To a 1,4-dioxane solution (0.1 M) of 6-bromo-5-iodopyrrolizine **1a** (0.2 mmol, 100 mol %) was added $Pd(PPh_3)_4$ (0.02 mmol, 10 mol %) at rt under argon atmosphere. After stirring for 20 min, K_2CO_3 (0.4 mmol, 200 mol %) in H_2O (0.15 M) and arylboronic acid (0.22 mmol, 110 mol %) were added. The mixture was stirred at 80 °C for 12 h. After cooling to rt, the mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ followed by brine. And then, the mixture was dried over $MgSO_4$ and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by flash column chromatography to provide the desired product, 5-aryl-6-bromopyrrolizine.

General Procedure for the Sequential 2nd Suzuki Cross-coupling Reactions. To a 1,4-dioxane solution (0.1 M) of 6-bromo-5-(3-nitrophenyl)pyrrolizine **3** (0.2 mmol, 100 mol %) was added $Pd(PPh_3)_4$ (0.02 mmol, 10 mol %) at rt under argon atmosphere.

After stirring for 20 min, K_2CO_3 (0.4 mmol, 200 mol %) in H_2O (0.15 M) and arylboronic acid (0.3 mmol, 150 mol %) were added. The mixture was stirred at 100 °C for 12 h. After cooling to rt, the mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ followed by brine. And then, the mixture was dried over $MgSO_4$ and filtered through a short Celite pad. The solution was concentrated in vacuo and the residue was purified by flash column chromatography to provide the desired product, 6-aryl-5-(3-nitrophenyl)pyrrolizine.

The Spectroscopic Data of 3 and 5-14 are as Follows.

Compound 3: yellow solid, mp 123 - 124 °C; IR (neat) 3446, 2948, 1716, 1533, 1349, 1283, 1179, 1081, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35-8.34 (m, 1H), 8.25-8.22 (m, 1H), 7.84-7.82 (m, 1H), 7.64 (t, J = 8.0 Hz, 1H), 6.36 (s, 1H), 4.89-4.83 (m, 1H), 4.23-4.20 (m, 1H), 4.00-3.94 (m, 1H), 3.63 (s, 1H), 2.75-2.71 (m, 1H), 2.48-2.45 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 135.1, 133.4, 131.9, 129.6, 125.1, 123.8, 122.7, 124.4 (q, $^1J_{CF}$ = 278.0 Hz), 105.7, 100.4, 77.6 (q, $^2J_{CF}$ = 32.0 Hz), 59.8, 55.8, 55.1, 20.4; HRMS calcd for [M] $C_{16}H_{14}BrF_3N_2O_4$ 434.0089, found 434.0091.

Compound 5: light yellow solid, mp 82 - 83 °C; IR (neat) 3423, 2930, 1734, 1708, 1532, 1349, 1160, 1082, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.22 (m, 1H), 8.19-8.18 (m, 1H), 8.01-7.98 (m, 2H), 7.62-7.55 (m, 2H), 7.40-7.32 (m, 2H), 6.46 (s, 1H), 4.89-4.83 (m, 1H), 4.26-4.22 (m, 1H), 4.03-3.97 (m, 1H), 3.92 (s, 1H), 2.82-2.79 (m, 1H), 2.72-2.69 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 148.2, 137.0, 135.8, 134.2, 133.9, 133.0, 130.0, 129.3, 126.6, 124.6 (q, $^1J_{CF}$ = 281.0 Hz), 124.5, 124.1, 123.0, 122.6, 120.9, 102.7, 77.2 (q, $^2J_{CF}$ = 32.0 Hz), 59.9, 55.6, 54.8, 20.6; HRMS calcd for [M] $C_{22}H_{18}F_3N_3O_6$ 477.1148, found 477.1151.

Compound 6: colorless oil; IR (neat) 3399, 2933, 1708, 1468, 1284, 1175, 1079, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.35 (m, 5H), 6.30 (s, 1H), 4.83-4.78 (m, 1H), 4.16-4.12 (m, 1H), 3.94 (s, 1H), 3.93-3.87 (m, 1H), 2.85-2.82 (m, 1H), 2.69-2.66 (m, 1H), 1.06 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 130.2, 129.2, 128.4, 128.0, 127.8, 124.5 (q, $^1J_{CF}$ = 284.0 Hz), 105.1, 98.9, 77.6 (q, $^2J_{CF}$ = 32.0 Hz), 59.8, 55.5, 55.2, 20.1; HRMS calcd for [M] $C_{16}H_{15}BrF_3NO_2$ 389.0238, found 389.0239.

Compound 7: colorless oil; IR (neat) 3399, 2961, 1709, 1466, 1276, 1182, 1092, 833, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.05 (m, 5H), 6.30 (s, 1H), 4.70-4.66 (m, 1H), 4.14-4.09 (m, 1H), 3.89-3.83 (m, 1H), 3.85 (s, 1H), 2.89-2.83 (m, 2H), 1.43-1.30 (m, 2H), 1.19-1.06 (m, 1H), 1.04-0.90 (m, 1H), 0.67 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 132.6, 130.2, 128.8, 128.7, 126.5, 124.5 (q, $^1J_{CF}$ = 282.0 Hz), 105.3, 99.4, 77.7 (q, $^2J_{CF}$ = 32.0 Hz), 60.9, 59.2, 51.8, 34.9, 16.7, 13.5; HRMS calcd for [M] $C_{18}H_{18}BrClF_3NO_2$ 451.0162, found 451.0160.

Compound 8: colorless oil; IR (neat) 3419, 2961, 1709, 1437, 1279, 1176, 1083, 822, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 7.25-7.21 (m, 2H), 6.28 (s, 1H), 4.69-4.65 (m, 1H), 4.13-4.06 (m, 1H), 4.01 (s, 1H), 3.88-3.81 (m, 1H), 2.90-2.85 (m, 2H), 2.39 (s, 3H), 1.38-1.21 (m, 2H), 1.14-1.04 (m, 1H), 1.03-0.92 (m, 1H), 0.64 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 131.9, 129.2, 128.8, 127.9, 127.2, 126.0, 124.6 (q, $^1J_{CF}$ = 281.0 Hz), 123.2, 104.9, 98.7, 77.4 (q, $^2J_{CF}$ = 32.0 Hz), 60.9, 59.1, 51.8, 34.6, 21.3, 16.6, 13.5; HRMS calcd for [M] $C_{19}H_{21}BrF_3NO_2$ 431.0708, found 431.0706.

Compound 9: colorless oil; IR (neat) 3422, 2937, 1709, 1614, 1476, 1287, 1250, 1176, 1033, 836, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 6.99-6.95 (m, 2H), 6.30 (s, 1H), 4.78-4.74 (m, 1H), 4.15-4.12 (m, 1H), 3.93-3.87 (m, 1H), 3.86 (s, 3H), 3.69 (s, 1H), 3.24 (dd, J = 10.0, 3.2 Hz, 1H), 3.19-3.16 (m, 1H), 3.08 (s, 3H), 3.04 (dd, J = 9.6, 6.8 Hz, 1H), 2.79 (dd, J = 8.0, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 132.8, 130.9, 128.2, 125.1 (q, $^1J_{CF}$ = 280.0 Hz), 122.8, 114.4, 105.7, 99.3, 77.7 (q, $^2J_{CF}$ = 32.0 Hz), 71.3, 60.9, 59.4, 59.3, 55.7, 50.9; HRMS calcd for [M] $C_{18}H_{19}BrF_3NO_4$ 449.0450, found 449.0420.

Compound 10: light yellow oil; IR (neat) 3410, 2932, 1709, 1595, 1464, 1282, 1176, 954, 852, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (m, 1H), 7.02-6.91 (m, 2H), 6.34 (s, 1H), 4.70-4.66 (m, 1H), 4.21 (s, 1H), 4.12 (dd, J = 11.6, 3.2 Hz, 1H), 3.91-3.87 (m, 2H), 3.27 (dd, J = 10.0, 3.6 Hz, 1H), 3.15-3.10 (m, 2H), 3.06 (s, 3H), 2.84-2.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (dd, $^1J_{CF}$ = 250.0 Hz, $^3J_{CF}$ = 12.0 Hz), 160.3 (dd, $^1J_{CF}$ = 249.0 Hz, $^3J_{CF}$ = 12.0 Hz), 133.4, 133.3, 124.4 (q, $^1J_{CF}$ = 280.0 Hz), 121.2, 114.4 (dd, $^2J_{CF}$ = 16.0 Hz, $^4J_{CF}$ = 4.0 Hz), 111.6 (dd, $^2J_{CF}$ = 22.0 Hz, $^4J_{CF}$ = 4.0 Hz), 105.4, 104.3 (dd, $^2J_{CF}$ = 26.0 Hz, $^2J_{CF}$ = 25.0 Hz), 101.0, 77.6 (q, $^2J_{CF}$ = 32.0 Hz), 71.0, 60.2, 59.7, 58.9, 50.1; HRMS calcd for [M] $C_{17}H_{15}BrF_5NO_3$ 455.0155, found 455.0156.

Compound 11: yellow solid, mp 171 - 172 °C; IR (neat) 3419, 2933, 1735, 1532, 1351, 1287, 1151, 1107, 950, 772, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.16 (m, 2H), 7.60-7.58 (m, 1H), 7.51-7.47 (m, 1H), 7.24-7.17 (m, 3H), 7.14-7.12 (m, 2H), 4.90-4.83 (m, 1H), 4.25-4.20 (m, 1H), 4.03-3.96 (m, 1H), 3.41 (s, 1H), 2.81-2.77 (m, 1H), 2.54 (dd, J = 7.6, 4.4 Hz, 1H), 1.09 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 135.9, 135.2, 133.8, 133.6, 129.6, 129.3, 128.4, 128.2, 126.3, 124.6 (q, $^1J_{CF}$ = 279.0 Hz), 124.0, 123.8, 122.3, 102.9, 77.3 (q, $^2J_{CF}$ = 32.0 Hz), 60.0, 55.8, 54.7, 20.7; HRMS calcd for [M] $C_{22}H_{19}F_3N_2O_4$ 432.1297, found 432.1298.

Compound 12: yellow solid, mp 148 - 149 °C; IR (neat) 3418, 2888, 1734, 1533, 1497, 1349, 1168, 1152, 1045, 950, 838, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.16 (m, 2H), 7.58-7.49 (m, 2H), 7.17-7.15 (m, 2H), 7.04-7.02 (m, 2H), 6.34 (s, 1H), 4.87-4.80 (m, 1H), 4.22-4.19 (m, 1H), 4.01-3.95 (m, 1H), 3.84 (s, 1H), 2.79-2.77 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 135.9, 133.8, 133.7, 133.5, 132.1, 129.7, 129.4, 128.6, 128.0, 124.6 (q, $^1J_{CF}$ = 281.0 Hz), 124.0, 123.9, 122.5, 102.7, 77.3 (q, $^2J_{CF}$ = 31.0 Hz), 59.9, 55.7, 54.7, 20.6; HRMS calcd for [M] $C_{22}H_{18}ClF_3N_2O_4$ 466.0907, found 466.0904.

Compound 13: yellow solid, mp 90 - 91 °C; IR (neat) 3394, 2888, 1532, 1349, 1285, 1170, 1152, 1043, 950, 797, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.14 (m, 2H), 7.60-7.57 (m, 1H), 7.51-7.47 (m, 1H), 7.03-6.99 (m, 4H), 6.35 (s, 1H), 4.88-4.82 (m, 1H), 4.23-4.18 (m, 1H), 4.01-3.95 (m, 1H), 3.54 (s, 1H), 2.80-2.76 (m, 1H), 2.67 (dd, J = 7.6, 4.4 Hz, 1H), 2.30 (s, 3H), 1.09 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 135.9, 134.0, 133.5, 132.2, 129.5, 129.4, 129.1, 128.1, 124.6 (q, $^1J_{CF}$ = 283.0 Hz), 124.0, 123.7, 122.2, 102.8, 77.3 (q, $^2J_{CF}$ = 31.0 Hz), 60.0, 55.8, 54.6, 21.0, 20.7; HRMS calcd for

[M] $C_{23}H_{21}F_3N_2O_4$ 446.1453, found 446.1456.

Compound 14: light brown solid, mp 63 - 64 ^{o}C; IR (neat) 3428, 2937, 1708, 1533, 1349, 1247, 1170, 1035, 836, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.14 (m, 2H), 7.59-7.57 (m, 1H), 7.51-7.47 (m, 1H), 7.06-7.03 (m, 2H), 6.77-6.75 (m, 2H), 6.33 (s, 1H), 4.91-4.82 (m, 1H), 4.23-4.20 (m, 1H), 4.02-3.95 (m, 1H), 3.77 (s, 3H), 3.59 (s, 1H), 2.80-2.76 (m, 1H), 2.70-2.64 (m, 1H), 1.09 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 148.3, 135.9, 133.9, 133.5, 129.5, 129.3, 128.9, 127.7, 124.7 (q, $^{1}J_{CF}$ = 282.0 Hz), 123.9, 123.4, 122.1, 113.8, 102.7, 77.2 (q, $^{2}J_{CF}$ = 31.0 Hz), 60.0, 55.7, 55.1, 54.6, 20.7; HRMS calcd for [M] $C_{23}H_{21}F_3N_2O_5$ 462.1403, found 462.1399.

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