A Solvent-Induced Reversal of Regioselectivity in the Suzuki Coupling of Pyrrole Esters

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Abstract: During a study of the regioselectivity of the Suzuki coupling of dihalopyrrole esters, the first instance of a reversal of regioselectivity based upon a change in reaction solvent has been observed. It is believed that this change in regioselectivity is due to a change in solvation of the pyrrole ester, since a change in chemical shift values is observed for the C3 and C5 protons upon going from DMF to chloroform to 3:1 benzene/methanol. An attempted application of this regioselectivity to the synthesis of the lamellarin family of natural products is reported as well.

INTRODUCTION

An ongoing focus of research in the Handy group has been the development of a one-pot polycoupling approach to substituted heteroaromatics. [1] The basic concept is to perform multiple couplings in a regiocontrolled, sequential fashion on a polyhalo starting material. The advantages of this approach are that it maintains the flexibility and functional group tolerance inherent in modern cross-coupling reactions, but decreases the number of steps required in a strictly sequential coupling approach to only one halogenation and one coupling event (Fig. **1**). [2]

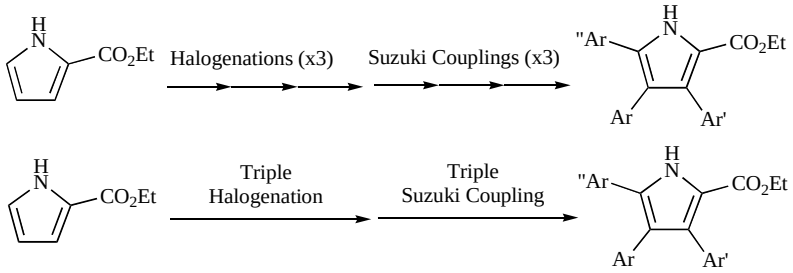

Fig. (1). The Polycoupling Concept.

One key question in this approach was being able to predict the regioselectivity in each of these coupling events. We have previously reported a predictive method that is based on the ^{1}H NMR chemical shift data for the starting, non-halogenated heteroaromatic. [3] This method has worked very well in predicting the results of reactions reported in the literature as well as additional reactions conducted in these labs, including previous studies of the coupling of dihalopyrrole esters. [1] Most of these substrates behaved in a normal predictable fashion, with the exception of the 4-aryl-3,5-dibromopyrrole esters, such as **1** (Table **1**). The unexpected results from these couplings are the subject of this paper.

RESULTS AND DISCUSSION

Dibromide **1** was a particularly interesting compound. Originally it had been obtained as an undesired by-product from some halogenation reactions in our synthetic studies targeting the lamellarins. [4] Since it could also be reliably prepared in good yield and would afford a direct regiocontrolled dicoupling route to the lamellarins that would be shorter than previous approaches, the conditions required for such a coupling were investigated. Initial efforts noted that tetrakis(triphenylphosphine)palladium(0) was the optimal catalyst and aqueous sodium carbonate was the optimal base, all using a 3:1 mixture of toluene and ethanol as the reaction solvent. Further optimization next focussed on the reaction solvent. Much to our surprise, simply changing the reaction solvent to DMF afforded modest selectivity for monocoupling product **3**, the regioisomer of **2**. Stunned by this observation, a number of different solvents were studied, the results of which are seen in Table **1**. On the surface, it appeared that more polar solvents generally favored formation of product **3**, while less polar solvents favored product **2**. Curiously, attempts to perform the reaction in toluene alone failed to afford any coupling, just recovered **1**. Further, making any significant comments regarding the influence of solvent polarity on the regioselectivity was made more difficult by the presence of a significant amount of water associated with the aqueous base solution. [5]

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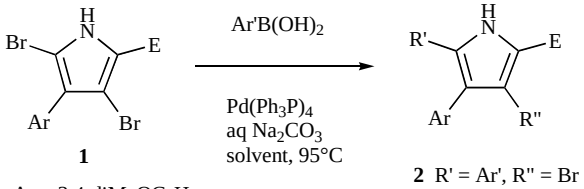
In attempting to determine the cause of this solvent effect on regioselectivity, two main hypotheses could be envisioned. In one case, the nitrogen on the pyrrole could serve to direct insertion of the palladium to the C5 bromide. [6] This coordination would then be possible in the ethanol/toluene mixture, but be disrupted in the more polar DMF or DMSO systems due to their greater Lewis basicity.

A second option was that differential solvation of the starting material resulted in a change of the electronics of C3 and C5. This line of reasoning was supported by ^{1}H NMR studies of the non-halogenated precursor to dibromide **1** in different solvents. [7] In deuterochloroform, the chemical shift difference between these two centers is barely detectible (0.08 ppm). On going to d6-DMSO, the C3 proton became clearly more electron deficient (more deshielded), with a chemical shift difference of 0.15 ppm between it and the C5 proton. On the other hand, in a 3:1 mixture of d6-benzene and d4-methanol, the C5 proton became more deshielded,

Table 1. Solvent Influence on Product Ratio



1

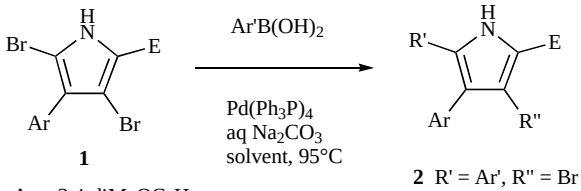
Ar = 3,4-diMeOC$_6$H$_3$
E = CO_2Et
Ar' = p-MeOC$_6$H$_4$

2 R' = Ar', R" = Br
3 R' = Br, R" = Ar'

Entry	Solvent	Yield[a]	Ratio (2:3)[b]
1	Toluene/Ethanol (3:1)	29/70/--	22:1
2	Acetonitrile	30/45/17	1:2
3	Dioxane	60/31/6	2:3
4	DMF	--/57/33	1:3
5	DMSO	37/50/10	1:4
6	Nitromethane	No rxn	NA
7	Toluene	No rxn	NA

[a] Isolated yield of starting material/monocoupled product (**2** and **3**)/dicoupled product. [b] Ratio determined by ^{1}H NMR.

Table 2. Influence of Boronic Acid on Product Ratio



1

Ar = 3,4-diMeOC$_6$H$_3$
E = CO_2Et

2 R' = Ar', R" = Br
3 R' = Br, R" = Ar'

Entry	Boronic Acid (Ar')	Solvent	Isolated Yield [a] (%)	Ratio[b] (2:3)
1	pMeOC$_6$H$_4$	Toluene/Ethanol	70	22:1
2	pMeOC$_6$H$_4$	DMF	53	1:3
3	oMeOC$_6$H$_4$	Toluene/Ethanol	57	6:1
4	oMeOC$_6$H$_4$	DMF	57	1:3
5	pAcC$_6$H$_4$	Toluene/Ethanol	53	20:1
6	**10**[c]	Toluene/Ethanol	68	10:1

[a] Mixture of both isomers. [b] Ratio determined by ^{1}H NMR. [c] **10** = 2-(3',4'-dimethoxyphenyl)ethanol.

with a wider gap of 0.25 ppm between it and the C3 proton. [8].

Beyond the obvious question regarding why this solvent dependence was observed for the couplings of **1**, there was also the question of how general this method would be. To that end, compound **1** was subjected to Suzuki couplings with a range of arylboronic acids, including electron rich and electron deficient ones. (Table **2**) In all cases, the ethanol/toluene solvent mixture afforded good to excellent selectivity for coupling at C5, while the use of DMF as the solvent afforded modest selectivity for coupling at C3. Some reduction in C5 selectivity was observed with the use of an ortho-substituted boronic acid, but the corresponding loss of C3 selectivity for reactions run in DMF was not observed (entries 3 and 4).

The impact of the C4-aryl group was also examined. Electron deficient aryl groups such as 3,4-difluorophenyl or p-acetylphenyl continued to afford the same selectivity trends. (Table **3**) Interestingly, very little change in the product ratio were observed for either of these new 4-aryl groups. This observation appears to indicate that the electronic influence of this 4-aryl group is surprisingly insignificant in these systems, perhaps indicating that the presence of the two bromides at C3 and C5 sterically hinder the ability of the 4-aryl group and the pyrrole core to be sufficiently co-planar for overlap of the two pi systems.

With this regioselective coupling in hand, it was applied to a potential second generation synthesis of the lamellarins. Thus, dibromide **1** was coupled first with boronic acid **10** and then dimethoxyphenylboronic acid to afford compound **11**. The plan was then to intercept compound **12**, an intermediate in Steglich's synthesis of Lamellarin G trimethyl ether. [9]. (Fig. **2**) Initially, this double coupling did not appear to be very promising since the second coupling failed to occur using just ethanol/toluene as the solvent. Fortunately, the addition of a co-solvent with the second boronic acid and an increase in the reaction temperature to 120 °C overcame this problem, with DMF affording 33% and DMSO affording 36% of product **11**.

From compound **11**, ring closure using the conditions reported in our initial synthesis of Lamellarin G trimethyl ether proceeded cleanly. [10] Unfortunately, hydrolysis of the ethyl ester to afford compound **12** failed to afford significant quantities of the acid, even under vigorous conditions. This situation can likely be overcome by using either a methyl or tert-butyl ester, both of which can be hydrolyzed under different conditions. From there, oxidative lactonization would complete the synthesis.

CONCLUSIONS

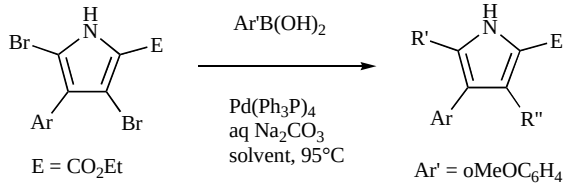
In conclusion, we have noted the first case of a solvent-induced change in regioselectivity in the coupling of polyhaloheteroaromatics. This shift is likely limited to cases in which there is relatively little intrinsic electronic different between the two centers as well as Lewis acidic or basic sites since no similar reversals have been observed in our work on pyridines and 2-formylthiophene. [1] Nevertheless, there are other similarly unbiased systems and it is certainly worth bearing in mind the influence of solvent for future studies of regioselectivity in cross-coupling reactions. [11].

EXPERIMENTAL

3,5-dibromo-4-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (1)

A solution of 380 mg (1.38 mmol) of 4-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester in 15 mL of DMF was chilled to 0 °C. To this solution was added 516.5 mg (2.90 mmol) of NBS portionwise. The reac-

Table 3. Influence of 4-Aryl Group on Regioselectivity



E = CO_2Et

Ar' = $oMeOC_6H_4$

4 Ar = 3,4-$DiFC_6H_3$
5 Ar = p-AcC_6H_4

6 Ar = 3,4-$DiFC_6H_3$ R' = Ar', R" = Br
7 Ar = 3,4-$DiFC_6H_3$ R' = Br, R" = Ar'
8 Ar = p-AcC_6H_4 R' = Ar', R" = Br
9 Ar = p-AcC_6H_4 R' = Br, R" = Ar'

Entry	Aryl Group (Ar)	Solvent	Yield[a]	Ratio[b] (6:7 or 8:9)
1	3,4-$DiFC_6H_3$	Toluene/Ethanol	39/52/-	10:1
2	3,4-$DiFC_6H_3$	DMF	-/57/33	1:3
3	3,4-$DiFC_6H_3$	DMSO	-/56/29	1:3
4	pAcC_6H_4	Toluene/Ethanol	37/60/-	8:1
5	pAcC_6H_4	DMSO	-/46/42	1:4

[a] Isolated yield of starting material/monocoupled product (**6**, **7**, **8**, or **9**)/dicoupled product. [b] Ratio determined by ^{1}H NMR.

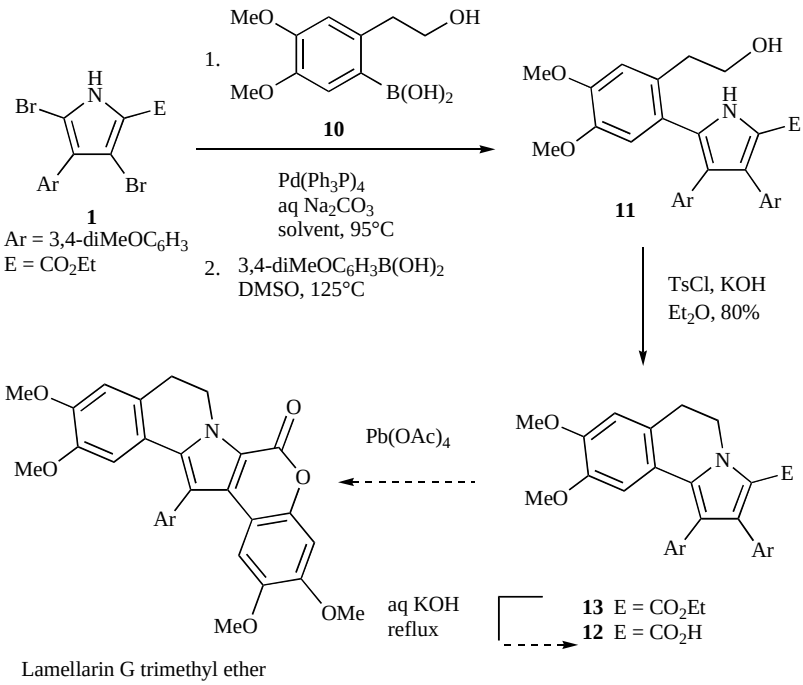


Fig. (2). Potential Formal Synthesis of Lamellarin G Trimethyl Ether.

tion was allowed to warm to room temperature overnight. The reaction was quenched with 30 mL of water and extracted with EtOAc (3 x 20 mL). The combined organic layers were separated, washed sequentially with aqueous $Na_2S_2O_3$, water, and brine, and concentrated *in vacuo* to afford 494 mg (83%) of **1** as a white solid. Mp = 126-128°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.97-6.92 (m, 3H), 4.42 (q, 2H, J = 7.2), 3.91 (s, 3H), 3.89 (s, 3H), 1.40 (t, 3H, J = 7.2), pyrrole NH not observed; ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.1, 148.5, 148.3, 126.5, 124.3, 122.7, 121.6, 113.4, 110.7, 104.6, 104.0, 61.4, 55.9, 55,7, 14.3; IR (neat) 3234 (s), 2930 (m), 1679 (s), 1584 (w), 1550 (w), 1520 (w), 1479 (m), 1436 (m), 1353 (m), 1246 (s), 1138 (m), 1028 (m), 766 (w). HRMS (EI) calcd for $C_{15}H_{15}Br_2NO_4$ 430.9368, found 430.9369.

3-bromo-4-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (2)

To a solution of 20 mg (0.046 mmol) of **1**, 7.7 mg (0.051 mmol) of *para*-methoxyphenylboronic acid, and 1.1 mg (0.0009 mmol) of tetrakis(triphenylphosphine) palladium(0) in 0.3 mL of toluene/ethanol (3:1) was added 0.05 mL 2 M sodium carbonate. The reaction was stirred at 95°C for 30 h. The reaction was quenched with 3 mL of water and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with water and brine and dried with magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was purified on silica gel, using 1:3 EtOAc-hexanes to afford 14.9 mg (70%) of **2** as a white solid, along with 5.8 mg (29%) of unreacted **1**. Mp = 133-134°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.22 (br s, 1H), 7.16 (d, 2H, J = 7.2), 6.85-6.77 (m, 5H), 4.38 (q, 2H, J = 7.2), 3.94 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 1.40 (t, 3H, J = 6.8); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.3, 159.4, 148.5, 148.1, 133.0, 128.6 (2 C's), 125.9, 124.8, 123.3, 123.0, 114.0 (2 C's), 113.8, 110.8, 106.9, 105.4, 60.7, 55.8, 55.7, 55.2, 14.4; IR (neat) 3277 (s), 2994 (m), 2835 (w), 2671 (s), 1621 (w), 1582 (w), 1557 (w), 1523 (s), 1464 (s), 1439 (m), 1418 (w), 1295 (m), 1253 (s), 1205 (m), 1138 (m), 1029 (s), 834 (w), 731 (w). HRMS (EI) calcd for $C_{22}H_{22}BrNO_5$ 459.0681, found 459.0679.

3-bromo-4-(3,4-dimethoxyphenyl)-5-(2-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester

Following the same procedure as for compound **2**, 20 mg (0.046 mmol) of **1**, 8.4 mg (0.055 mmol) of 2-methoxyphenylboronic acid were used. 12.0 mg (57%) was obtained. ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.15 (br s, 1H), 7.27-7.24 (m, 1H), 7.00 (d, 1H, J = 1.4), 6.96 (d, 1H, J = 1.0), 6.86-6.83 (m, 2H), 6.77-6.75 (m, 2H), 4.39 (q, 2H, J = 7.6), 3.90 (s, 3H), 3.88 (s, 3H), 3.75 (s, 3H), 1.40 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.1, 148.5, 148.0, 130.4, 129.7, 129.1, 126.7, 122.9, 122.6, 120.7, 113.7, 113.3, 111.2, 110.9, 110.7, 106.3, 105.4, 60.6, 55.8, 55.7, 55.6, 14.4; IR (neat) 3278 (m), 2954 (m), 2930 (m), 1718 (s), 1583 (w), 1522 (w), 1465 (s), 1432 (w), 1251 (s), 1138 (w), 1027 (m), 765 (w). HRMS (EI) calcd for $C_{22}H_{22}BrNO_5$ 459.0681, found 459.0680.

5-(4-acetylphenyl)-3-bromo-4-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester

Following the same procedure as for compound **2**, 20 mg (0.046 mmol) of **1** and 9.1mg (0.55 mmol) of 4-acetylphenylboronic acid were used. 11.6 mg (53.2%) was obtained. ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.39 (br s, 1H), 7.82 (d, 2H, J = 8.3), 7.28 (d, 2H, J = 8.6) 6.74-6.72 (m, 2H), 6.51 (s, 1H), 4.36 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 3.76 (s, 3H), .6 (s, 3H), 1.38 (t, 3H, J = 7.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.8, 159.8, 148.2, 147.9, 138.8, 135.5, 140.0, 128.7, 127.5, 124.6, 122.4, 120.9, 113.4, 111.2, 110.7, 104.2, 60.7, 55.8, 55.6, 31.8, 14.0; IR (neat) 3257 (m), 2925 (m), 1680 (s), 1606 (m), 1524 (w), 1403 (m), 1378 (m), 1335 (w), 1245 (s), 1181 (m), 1139 (w), 1026 (m), 859 (w), 765 (w).

HRMS (EI) calcd for $C_{23}H_{22}BrNO_5$ 471.0681, found 471.0682.

3-bromo-4-(3,4-dimethoxyphenyl)-5-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester

Following the same procedure as for compound **2**, 30 mg (0.069 mmol) of **1** and 39.1 mg (0.173 mmol) of boronic acid **10** were used, and 25.0 mg (68%) was obtained. ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.93 (br s, 1H), 7.09 (s, 1H), 6.78 – 6.72 (m, 3H), 6.64 (s, 1H), 4.30 (q, 2H, J = 7.2), 3.93 (t, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.67 (s, 3H), 3.55 (s, 3H), 2.80 (t, 2H), 1.35 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.5, 149.1, 148.4, 147.1, 147.1, 132.1, 130.2, 128.2, 124.7, 123.8, 121.6, 120.0, 114.6, 114.1, 112.2, 111.1, 110.9, 63.7, 60.3, 55.8, 55.7, 55.6, 35.0, 29.6, 14.4; IR (neat) 3439 (w, br), 3292 (w, br), 2927 (m), 2850 (w), 1699 (s), 1607 (w), 1560 (w), 1522 (s), 1466 (s), 1438 (m), 1381 (w), 1242 (s), 1208 (s), 1140 (m), 1026 (m), 860 (w), 730 (w). HRMS (EI) calcd for $C_{25}H_{28}BrNO_7$ 535.1206, found 535.1205.

5-bromo-4-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (3)

To a solution of 20 mg (0.046 mmol) of **1**, 8.4 mg (0.055 mmol) of *para*-methoxyphenylboronic acid, and 2.6 mg (0.001 mmol) of tetrakis(triphenylphosphine) palladium(0) in 0.4 mL of DMF was added 0.05 mL 2 M sodium carbonate. The reaction was stirred at 95°C for 20 h. The reaction was quenched with 3 mL of water and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with water and brine and dried with magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was purified on silica gel, using 1:3 EtOAc-hexanes to afford 10.4 mg (53%) of **3** as a white solid. Mp = 116-117°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 7.10 (d, 2H, J = 7.2), 6.80-73 (m, 4H), 6.53 (s, 1H), 4.21 (q, 2H, J = 7.2), 3.86 (s, 3H), 3.78 (s, 3H), 3.59 (s, 3H), 1.18 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.2, 158.6, 148.0, 147.6, 131.8, 122.6, 122.3, 119.9, 114.0, 113.9, 113.6, 113.4, 112.8, 110.6, 103.8, 60.4, 55.8, 55.6, 55.1, 14.0; IR (neat) 3270 (m), 2933 (w), 1669 (s), 1611 (w), 1531 (m), 1508 (w), 1464 (m), 1417 (m), 1439 (w), 1380 (w), 1245 (s), 1178 (s), 1139 (m), 1028 (m), 833 (w). HRMS (EI) calcd for $C_{22}H_{22}BrNO_5$ 459.0681, found 459.0681.

5-bromo-4-(3,4-dimethoxyphenyl)-3-(2-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester

Following the same procedure as for compound **3**, 20 mg (0.046 mmol) of **1** and 8.4 mg (0.055 mmol) of 2-methoxyphenylboronic acid were used. 11.7 mg (57%) was obtained. ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.39 (br s, 1H), 7.23 (d, 1H, J = 7.2), 7.11 (d, 1H, J = 7.2), 6.87-6.75 (m, 4H), 6.54 (s, 1H), 4.14 (q, 2H, J = 3.6), 3.82 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H), 1.10 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 157.1, 147.8, 147.4, 132.2, 130.4, 129.7, 126.7, 125.4, 123.1, 121.4, 120.7, 113.7, 113.3, 111.2, 110.7, 110.6, 106.4, 60.2, 55.7, 55.6, 55.5, 14.0; IR (neat) 3271 (w), 2930 (m), 1774 (s), 1584 (w), 1548 (w), 1519 (w), 1467 (w), 1439 (s), 1372 (m), 1310 (m), 1255 (s), 1144 (s), 1075 (m), 1027 (m), 842 (w), 764 (w). HRMS (EI) calcd for $C_{22}H_{22}BrNO_5$ 459.0681, found 459.0682.

3,5-dibromo-4-(3,4-difluorophenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (4)

To a solution of 480 mg (1.51 mmol) of 4-bromo-1*H*-pyrrole-2-carboxylic acid ethyl ester, 358 mg (2.27 mmol) of 3,4-difluorophenyl boronic acid and 87.5 mg (0.07 mmol) of tetrakis(triphenylphosphine) palladium(0) in 20 mL of DMF was added 7.0 mL of 2 M aqueous Na_2CO_3. The reaction mixture was stirred at 110°C for 15 hours. The reaction was quenched with 40 mL of water and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water and brine, and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was chromatographed on silica gel, using 1:3 EtOAc-hexanes, to afford 246.0 mg (65%) of the coupled product as a white solid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.25 (br s, 1H), 7.20-7.10 (m, 5H), 4.33 (q, 2H, J = 7.2), 1.37 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.1, 151.9, 150.3, 148.9, 147.5, 131.8, 124.8, 123.9, 121.0, 119.4, 117.4, 114.0, 112.2, 60.3, 14.3; IR (neat) 3265 (s), 2921 (w), 1679 (s), 1601 (w), 1572 (w), 1523 (w), 1488 (w), 1384 (m), 1297 (m), 1195 (s), 1147 (m), 769 (w).

A solution of 240 mg (0.956 mmol) of the above compound in 25 mL of DMF was chilled to 0°C. To this solution was added portionwise 349 mg (1.96 mmol) of NBS. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with 40 mL of water and extracted with EtOAc (3 x 30 mL). The combined organic layers were separated and washed sequentially with saturated aqueous $Na_2S_2O_3$, water and brine, and concentrated *in vacuo* to afford 342 mg (88%) of **4** as a white solid. Mp = 125-128°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 7.25 – 7.13 (m, 3H), 4.39 (q, 2H, J = 7.2), 1.39 (t, 3H, J = 6.0); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.1, 151.3, 148.6, 128.2, 126.5, 121.9, 119.2 (d, J^{CF} = 68.4 Hz), 117.0 (d, J^{CF} = 68.4 Hz), 115.0, 104.1, 103.7, 60.3, 14.0; IR (neat) 3232 (m), 1913 (w), 1676 (s), 1598 (m), 1544 (w), 1515 (w), 1472 (w), 1437 (m), 1382 (m), 1264 (s), 1237 (m), 1191 (m), 1116 (w), 872 (m), 816 (m). HRMS (EI) calcd for $C_{13}H_9Br_2F_2NO_2$ 392.8937, found 392.8938.

3-bromo-4-(3,4-difluorophenyl)-5-(2-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (6)

To a solution of 20 mg (0.049 mmol) of **4**, 8.9 mg (0.059 mmol) of 2-methoxyphenylboronic acid, and 2.8 mg (0.025 mmol) of tetrakis(triphenylphosphine) palladium(0) in 0.4 mL of toluene-ethanol (3:1) was added 0.1 mL of 2M aqueous Na_2CO_3. The reaction mixture was stirred at 95°C for 15 hours. The reaction was quenched with 5 mL of water and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water and brine, and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was purified on silica gel, using 1:4 EtOAc-hexanes, to afford 11.2 mg (52.0%) of **6** as a white solid. Mp = 131-132°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.02 (br s, 1H), 7.25-7.22 (m, 1H), 7.17-7.11 (m, 2H), 6.95-6.93 (m, 3H), 6.77-6.76 (m, 1H), 4.38 (q, 2H, J = 7.2), 3.84 (s, 3H), 1.40 (t, 3H, J = 3.6); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.1, 156.4, 151.0, 130.4, 130.1, 129.7, 126.8, 126.8, 126.7, 123.5, 120.8, 119.4 (d, J^{CF} = 68.4), 118.4, 117.1 (d, J^{CF} =

68.4), 111.4, 110.5, 104.8, 60.8, 55.5, 14.4; IR (neat) 3256 (w), 2924 (m), 1670 (s), 1603 (w), 1559 (m), 1506 (m), 1463 (s), 1403 (m), 1251 (s), 1216 (w), 1039 (w), 772 (w), 754 (w). HRMS (EI) calcd for $C_{20}H_{16}BrF_2NO_3$ 435.0281, found 435.0279.

5-bromo-4-(3,4-difluorophenyl)-3-(2-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (7)

To a solution of 20 mg (0.046 mmol) of **4**, 8.4 mg (0.055 mmol) of 2-methoxyphenylboronic acid, and 2.6 mg (0.0011 mmol) of tetrakis(triphenylphosphine) palladium(0) in 0.4 mL of DMF was added 0.05 mL 2 M sodium carbonate. The reaction was stirred at 95°C for 15 h. The reaction was quenched with 3 mL of water and extracted with EtOA (2 x 5 mL). The combined organic layers were washed with water and brine and dried with magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was purified on silica gel, using 1:3 EtOAc-hexanes to afford 12.0 mg (57%) of **7** as a white solid. Mp = 141-143°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.52 (br s, 1H), 7.25-6.80 (m, 7H), 4.14 (q, 2H, J = 7.2), 3.51 (s, 3H), 1.10 (t, 3H, J = 3.6); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.2, 156.9, 132.1, 130.4, 129.7, 129.6, 125.5, 122.1, 120.8, 120.0, 119.3, 118.1 (d, J^{CF} = 68.4), 117.2, 116.5 (d, J^{CF} = 68.4), 111.4, 110.5, 103.7, 60.4, 55.0, 14.0; IR (neat) 3247 (m), 2925 (m), 1671 (s), 1603 (w), 1533 (w), 1464 (s), 1406 (m), 1382 (m), 1251 (s), 1177 (w), 1117 (w), 1027 (m), 874 (w), 753 (w). HRMS (EI) calcd for $C_{20}H_{16}BrF_2NO_3$ 435.0281, found 435.0281.

DMSO CONDITIONS

Using the same conditions outlined above, but with 20 mg (0.049 mmol) of 4 and DMSO in place of DMF, 11.7 mg (55.3%) of **7** was obtained.

4-acetylphenyl-3,5-dibromo-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (5)

To a solution of 250 mg (0.79 mmol) of 4-bromo-1*H*-pyrrole-2-carboxylic acid ethyl ester, 194 mg (1.18 mmol) of 4-acetylphenylboronic acid and 45.6 mg (0.07 mmol) of tetrakis(triphenylphosphine) palladium(0) in 10 mL of DMF was added 4.0 mL of 2M aqueous Na_2CO_3. The reaction mixture was stirred at 110°C for 16 hours. The reaction was quenched with 20 mL of water and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water and brine, and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was chromatographed on silica gel, using 1:3 EtOAc-hexanes, to afford 145.0 mg (72%) of the coupling product as a white solid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.92 (br s, 1H), 7.92 (d, 2H, J = 7.2), 7.57 (d, 2H, J = 7.2), 7.33 (s, 1H), 7.23 (s, 1H), 4.33 (q, 2H, J = 7.2), 2.57 (s, 3H), 1.23 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.8, 161.1, 139.4, 134.6, 129.0, 125.3, 124.8, 124.0, 120.6, 112.5, 60.6, 26.4, 14.3; IR (neat) 3306 (m), 2926 (w), 1701 (s), 1678 (s), 1604 (s), 1577 (w), 1446 (w), 1379 (m), 1266 (s), 1211 (m), 1136 (m), 926 (w).

136 mg (0.53 mmol) of the above product in 20 mL of DMF was chilled to 0°C. To this solution was added portionwise 193 mg (1.08 mmol) of NBS. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with 20 mL of water and extracted with EtOAc (3 x 20 mL). The combined organic layers were separated and washed sequentially with saturated aqueous $Na_2S_2O_3$, water and brine, and concentrated *in vacuo* to afford 180 mg (82.0%) of **5** as a white solid. Mp = 116-118°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.85 (br s, 1H), 8.03 (d, 2H, J = 6.5), 7.54 (d, 2H, J = 8.3), 4.41 (q, 2H, J = 6.8), 2.64 (s, 3H), 1.41 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.7, 159.5, 136.7, 136.1, 130.3 (2 C's), 128.2 (2 C's), 125.7, 122.1, 104.5, 103.6, 61.4, 29.6, 14.3; IR (neat) 3222 (s), 2990 (w), 1672 (s), 1603 (m), 1559 (w), 1517 (w), 1440 (w), 1413 (w), 1381 (w), 1258 (s), 1204 (m), 1012 (w), 954 (w), 840 (w), 756 (w). HRMS (EI) calcd for $C_{15}H_{13}Br_2NO_3$ 412.9262, found 412.9263.

4-acetylphenyl-3-bromo-5-(2-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (8)

To a solution of 20 mg (0.048 mmol) of **5**, 8.8 mg (0.058 mmol) of 2-methoxyphenylboronic acid, and 2.8 mg (0.003 mmol) of tetrakis(triphenylphosphine) palladium(0) in 0.5 mL of toluene/ethanol (3:1) was added 0.1 mL 2 M sodium carbonate. The reaction was stirred at 95°C for 15 h. The reaction was quenched with 5 mL of water and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with water and brine, and then dried with magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was purified on silica gel, using 1:4 EtOAc-hexanes to afford 12.7 mg (60%) of **8** as a white solid. Mp = 122-123°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.03 (br s, 1H), 7.93 (d, 2H, 7.2), 7.38 (d, 2H, J = 7.2), 7.27-7.23 (m, 2H), 6.96-6.93 (m, 1H), 6.74-6.73 (m, 1H), 4.41 (q, 2H, J = 6.8), 3.82 (s, 3H), 2.62 (s, 3H), 1.42 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.9, 160.1, 139.5, 135.6, 130.7, 130.6, 130.3, 130.2, 129.7, 129.2, 128.3, 128.1, 127.8, 120.7, 111.4, 108.3, 60.8, 55.5, 26.6, 14.4; IR (neat) 3260 (w), 2924 (m), 1679 (s), 1605 (m), 1505 (w), 1474 (m), 1400 (w), 1264 (s), 1182 (m), 1040 (m), 955 (m), 757 (w). HRMS (EI) calcd for $C_{22}H_{20}BrNO_4$ 441.0576, found 441.0578.

4-acetylphenyl-5-bromo-3-(2-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (9)

To a solution of 20 mg (0.048 mmol) of **5**, 8.8 mg (0.058 mmol) of 2-methoxyphenylboronic acid, and 2.6 mg (0.0011 mmol) of tetrakis(triphenylphosphine) palladium(0) in 0.4 mL of DMSO was added 0.05 mL 2 M sodium carbonate. The reaction was stirred at 95°C for 10 h. The reaction was quenched with 3 mL of water and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with water and brine and dried with magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was purified on silica gel, using 1:4 EtOAc-hexanes to afford 9.9 mg (47%) of **9** as a white solid. Mp = 137-138°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 7.79 (d, 2H, J = 6.8), 2.24 (d, 2H, J = 6.8), 6.88 (m, 2H), 6.76 (m, 2H), 4.14 (q, 2H, J = 7.1), 3.43 (s, 3H), 2.54 (s, 3H), 1.38 (t, 3H, J = 7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.5, 159.8, 156.6, 135.0, 132.2, 130.7, 129.7, 129.2, 129.1, 128.3, 127.8, 125.7, 120.0, 111.4, 110.6, 105.8, 60.4, 55.0, 29.3, 14.1; IR (neat) 3246 (m), 2923 (m), 1671 (s), 1605 (m), 1495 (w), 1465 (m), 1397 (m), 1380 (m), 1354 (w), 1249 (s), 1180 (w), 1099 (w), 1026 (w), 953 (w), 835 (w), 754 (w). HRMS (EI) calcd for $C_{22}H_{20}BrNO_4$ 441.0576, found 441.0576.

3,4-Bis-(3,4-dimethoxyphenyl)-5-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (11)

To a solution of 20 mg (0.046 mmol) of **1**, 26.1 mg (0.115 mmol) of **10**, and 2.7 mg (0.0023 mmol) of $Pd(PPh_3)_4$ in 0.6 mL of toluene-ethanol (3:1), was added 0.2 mL of 2 M sodium carbonate. The reaction was stirred under argon at 95°C for 25 h. To the reaction was added 12.6 mg (0.069 mmol) of 3,4-dimethoxyphenylboronic acid, and 0.5 mL of DMSO. The reaction was stirred at 120°C for 20 h. To the reaction was added 5 mL of water and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water and brine, and dried with magnesium sulfate. The solvent was removed *in vacuo*. The resulting residue was chromatographed on silica gel, using 3:1 EtOAc-hexanes, to afford 9.8 mg (36%) of **11** as a solid. Mp = 111-113°C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 11.12 (br s, 1H), 6.82 – 6.76 (m, 3H), 6.57 (d, 1H, J = 7.2), 6.49 (s, 1H), 6.43-6.39 (m, 2H), 4.19 (q, 2H, J = 7.2), 4.02 (t, 2H, J = 6.8 Hz), 3.88 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 2.89 (t, 2H, J = 6.8 Hz), 1.23 (t, 3H, J = 7.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.5, 148.9, 148.1, 147.6, 146.8, 136.7, 133.2, 132.0, 130.0, 129.9, 127.3, 127.2, 125.8, 125.3 124.6, 123.4, 122.9, 114.5, 114.0, 111.9, 110.5, 110.1, 106.1, 64.0, 59.9, 55.8, 55.7, 55.6, 55.5, 55.4, 34.9, 29.6, 14.2; IR (neat) 3530 (w), 3233 (w), 2929 (m), 1685 (s), 1607 (w), 1557 (w), 1521 (s), 1464 (w), 1464 (m), 1434 (m), 1380 (m), 1243 (s), 1138 (m), 1115 (m), 1027 (s), 861 (w), 730 (w). HRMS (EI) calcd for $C_{33}H_{37}NO_9$ 591.2468, found 591.2469.

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REFERENCES

[1] S.T. Handy and J.J. Sabatini, *Org. Lett.*, **2006**, *8*, 1537. S.T. Handy and Y. Zhang, *Synthesis*, **2006**, 3883. S.T. Handy, T. Wilson, and A. Muth, *J. Org. Chem.*, **2007**, *72*, 8496. S.T. Handy and D. Mayi, *Tetrahedron Lett.*, **2007**, *48*, 8108.

[2] G.W. Gribble and J.J Li, "Palladium in Heterocyclic Chemistry" Elssevier: London, **2006**.

[3] S.T. Handy and Y. Zhang, *Chem. Commun.*, **2006**, 299.

[4] S.T. Handy, Y. Zhang, and H. Bregman, *J. Org. Chem.*, **2004**, *69*, 2362.

[5] It should be noted that reactions in the absence of water failed to afford any coupling products and only resulted in recovery of starting material.

[6] For examples of chelation-driven regioselectivity, see: F. Kakiuchi and S. Murai, *Activation of C-H Bonds: Catalytic Reactions* In "Activation of Unreactive Bonds and Organic Synthesis," S. Murai, Ed. Springer: Berlin, **1999**.

[7] A combination of HMBC and HMQC spectroscopy was employed to determine the signals corresponding to the C3 and C5 protons.

[8] The coupling of **1** in a 3:1 mixture of benzene and methanol afforded selectivity results indistinguishable from that of the toluene/ethanol mixture.

[9] A. Heim, A. Terpin, W. Steglich, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 155.

[10] S.T. Handy and Y. Zhang, *Org. Prep. & Proc. Int.* **2005**, *37*, 411.

[11] One possible application is thiophenes. K.O. Jeon, J.S. Yu, and C.K. Lee, *Heterocycles* **2003**, *60*, 2685. However, preliminary experiments have not demonstrated any solvent effect on the regioselectivity in coupling of 2,3-dibromothiophene or 2,4-dibromothiophene. These experiments will be reported in due course.

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