Suzuki–Miyaura Arylations of Tetramic Acid Sulfonates: Evaluation of Lactam Protection, Sulfonate Esters, and Sterics

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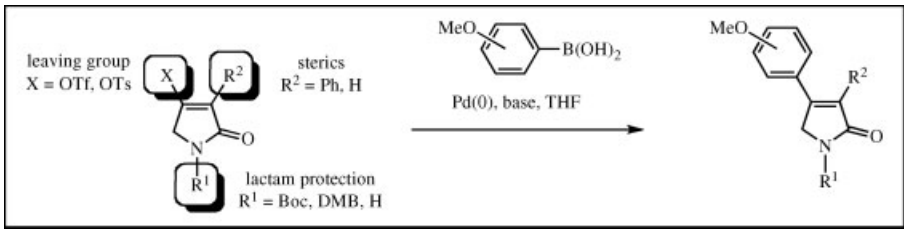

The synthesis of 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones using Suzuki–Miyaura cross-coupling reactions of tetramic acid sulfonates with arylboronic acids has been studied. The effect that sulfonate ester, sterics, and lactam protection has on the cross-coupling reaction was evaluated. As expected, triflates were better cross-coupling partners than the corresponding tosylates. The yields were only partially affected by the incorporation of aryl groups at the 3-position. Importantly, tetramic acid triflates (and to a lesser extent tosylates) lacking a lactam protecting group were still competent substrates.

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INTRODUCTION

3,4-Diaryl-3-pyrrolin-2-ones **1a** and 4-aryl-3-pyrrolin-2-ones **1b** are important synthetic targets given their range of biological activity and utility as precursors to other compounds. 3,4-Diaryl-3-pyrrolin-2-ones have been investigated as inhibitors of cyclooxygenase-II (COX-II) [1], vascular endothelial growth factor receptor (VEGF-R) [2], and protein kinase C (PKC) [3]. 3,4-Diaryl-3-pyrrolin-2-ones have been used as building blocks for the preparation of the PKC inhibitor staurosporinone [4] and *N*-protected staurosporinones [5], whereas 4-aryl-3-pyrrolin-2-ones have been used as intermediates in the synthesis of 4-arylpyrrolidinones [6] (*e.g.*, antidepressant rolipram) [7], γ-aminobutyric acids [8] (*e.g.*, antispastic agent baclofen) [9], and β-arylpyrroles [10]. Before our involvement in this field [11,12], nearly all of the known methods to aryl-substituted 3-pyrrolin-2-ones **1** involved linear sequences that culminated in aldol-like cyclocondensations of α-amidoketones **2** [1,2,4,5,10a,13] (Fig. 1). An alternate method that has been explored to prepare 3,4-diaryl-3-pyrrolin-2-ones **1a** involves reducing the corresponding maleimides with borane [3a], but these reactions have proven to be nonselective [14]. Alternate methods used to synthesize 4-aryl-3-pyrrolin-2-ones **1b** include treatment of 4-bromo-2-butenoates with amines [6,8,15] and ring expansion of cyclobutanones [10b]. These literature methods all incorporate the C-4 aryl groups early in the sequence making them less applicable to the synthesis of C-4 aryl analogs [16]. A four component Ugi reaction provided access to 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones, but this route was not amenable to the preparation of 5-unsubstituted derivatives [17,18].

Given their importance as drug candidates and building blocks, we initiated a program aimed at developing novel synthetic approaches to aryl-substituted 3-pyrrolin-2-ones that were amenable to the synthesis of new substitution patterns that allowed for the preparation of analogs. We recently reported our progress toward developing methodologies to **1** using Suzuki–Miyaura cross-coupling reactions of tetramic sulfonates **3a** [11a] and **4b** [11b] (Fig. 1). These methods have the potential to be useful in the synthesis of analogs given the late-stage introduction of C-4 aryl groups. The utility of our synthetic methodology was demonstrated by preparing the *N*-unsubstituted lactam analog of Vioxx® from **3a** and the 4-arylpyrrolidinone precursor to baclofen from **4b**.

We were initially inspired to investigate Suzuki–Miyaura cross-coupling reactions for the installation of C-4 aryl groups onto tetramic acid sulfonates by the analogous cross-coupling reactions of tetronic acid sulfonates **5** [19,20] and **6** [21] (Fig. 2). Interestingly, the cross-coupling of **6a** was reported to proceed in very low yield; this was attributed to a steric effect caused by the neighboring phenyl group [21a]. On the other hand, we observed excellent yields in the cross-coupling reactions of triflate **3a** which also contains a vicinal phenyl

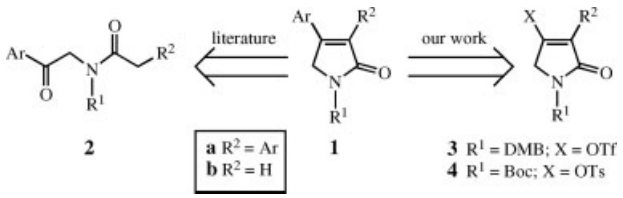


Figure 1. Synthetic approaches to 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones.

group [11a]. To better understand the limitations of our methodology, we decided to systematically study the effect that sterics (R^3 = Ph *vs.* R^3 = H), sulfonate ester [trifluoromethanesulfonyl (OTf) *vs.* tosylsulfonyl (OTs)], and lactam protecting group [*tert*-butoxycarbonyl (Boc) *vs.* 3,4-dimethoxybenzyl (DMB)] have on the yield of the cross-coupling reaction. We thus set out to prepare new tetramic acid sulfonates **7** and **8** and compare their competence as cross-coupling substrates to our known tetramic acid sulfonates **3** and **4**. Our progress to date is reported herein.

RESULTS AND DISCUSSION

Tetramic acid sulfonate ester substrates (*e.g.*, **3a**) [11a] were prepared from the corresponding 3-phenyltetramic acids. The latter can be obtained *via* Dieckmann-like cyclocondensations of the corresponding *N*-phenylacetylglycinates [22]. Toward this end, treatment of glycine ethyl ester (**9**) with phenacetyl chloride gave known amide **10** [23] (Scheme 1). Conversion of **10** to **11** was achieved with Boc_2O and 4-(*N*,*N*′-dimethylamino)pyridine (DMAP) [24]. 3-Phenyltetramic acid **12** was then prepared by a Dieckmann cyclocondensation of **11** mediated by sodium *tert*-butoxide. Treatment of **12** with either triflic anhydride or tosyl chloride in the presence of triethylamine gave **7a** and **4a**, respectively.

In some cases, the synthesis of **7a** was accompanied by the formation of small amounts of lactam **13a** *via* a seemingly facile Boc deprotection (this was not

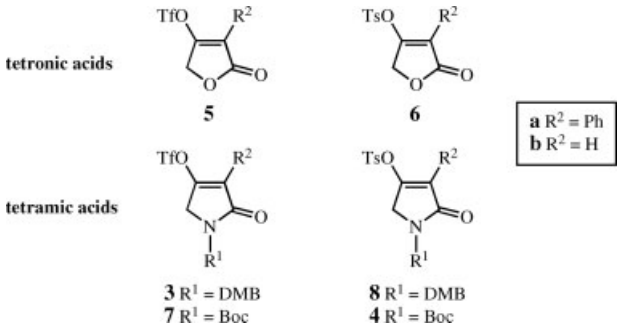
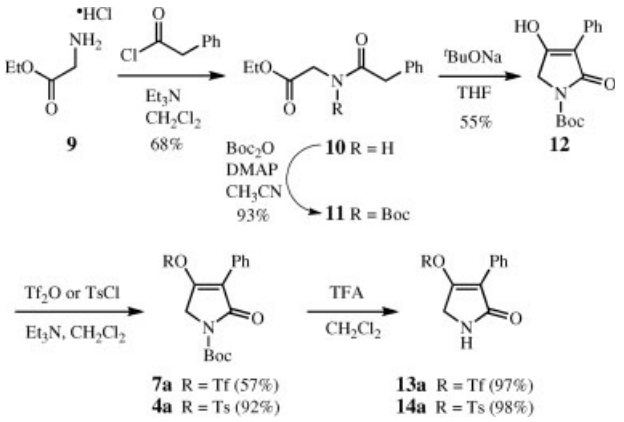


Figure 2. Tetramic acid sulfonates and tetronic acid sulfonates.

Scheme 1



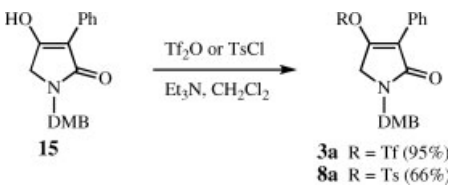
observed with **4a**). We therefore decided to investigate cross-coupling reactions of substrates that did not contain protecting groups. Thus, we treated **7a** and **4a** with trifluoroacetic acid (TFA), and obtained lactams **13a** and **14a**, respectively.

We reported a similar procedure for the synthesis of DMB-protected tetramic acid **15** [11a]. Treatment of **15** with either triflic anhydride or tosyl chloride in the presence of triethylamine gave **3a** [11a] and new compound **8a**, respectively (Scheme 2).

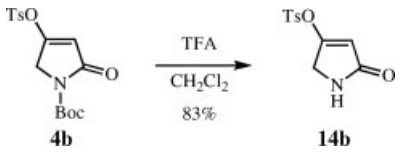
The next substrate that was prepared was *N*-unsubstituted tetramic acid tosylate **14b**. Known compound **4b** was available from our previous studies by the cyclocondensation of Boc-glycine with Meldrum's acid [11b,25]. Treatment of **4b** with TFA led to lactam **14b** (Scheme 3). We were not able to access 4-trifloxy-3-pyrrolin-2-one *via* this route as the requisite starting material, compound **7b**, turned out to be unstable and underwent a facile dimerization [11b].

With the tetramic acid sulfonate substrates in hand, we evaluated the effect that lactam protecting group, sulfonate leaving group, and sterics have on the yield of Suzuki–Miyaura cross-coupling reactions. We used our previously optimized conditions for cross-coupling reactions with tetramic acid triflates [Method A: $Pd(PPh_3)_4$ and Na_2CO_3] [11a] and tetramic acid tosylates [Method B: Pd(1,1-bis(diphenylphosphino)ferrocen)Cl_2(Pd(dppf)Cl_2), Cs_2CO_3] [11b]. To simplify our study and the analysis of the products, we used 4-methoxyphenylboronic acid. Our results are detailed later in Tables 1–3.

Scheme 2



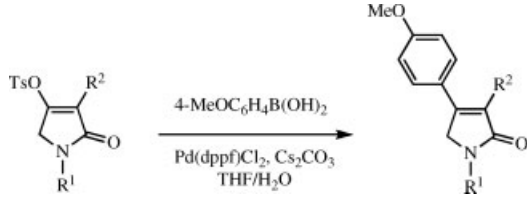
Scheme 3



We first examined the cross-coupling reactions of 3-phenyltetramic acid sulfonates (Table 1). The results shown in Table 1 describe the effect that lactam protecting group (R^1 = Boc *vs.* R^1 = DMB *vs.* R^1 = H) have on the cross-coupling reaction. These results also show the relative capabilities of the sulfonate leaving groups (X = OTf *vs.* X = OTs). In the triflate series, the Boc and DMB protecting groups were equivalent (97% *vs.* 95%); on the other hand in the tosylate series, the Boc protecting group proved to be superior (40% *vs.* Trace). We were pleasantly surprised to see that *N*-unsubstituted triflate **13a** proved to be a viable substrate providing known 3,4-diaryl-3-pyrrolin-2-one **18a** in 62% yield. This result indicates a potential for step savings that could be realized with this methodology during the preparation of analogs. Unlike triflate **13a**, cross-coupling with the corresponding *N*-unsubstituted tosylate **14a** failed to give product **18a**. As expected, triflate leaving groups proved to be superior to tosylate leaving groups; in some cases, triflate leaving groups appear to be required in the cross-coupling of unprotected lactams.

Next, we examined the cross-coupling reactions of tetramic acid tosylates **4** and **14** with 4-methoxyphenylboronic acid using Method B (Table 2). We used tosylates in this study as 3-unsubstituted triflates (R^2 = H) were not available. The results shown in Table 2 describe the effects of sterics (R^2 = Ph *vs.* R^2 = H) on the cross-coupling reactions. With Boc-protected tetramic acid tosylates **4**, the addition of a vicinal phenyl group lowered the yield (74% *vs.* 40%) although it did not shut down the reaction as was observed with the 3-phenyltetronic acid tosylate [21a]. Somewhat unexpectedly with *N*-unsubstituted tetramic acid tosylates **14**, the neighboring phenyl group precluded the reaction (55% *vs.* 0%). When further analyzing the importance of lactam protection, the yield was only partially diminished going from *N*-Boc tosylate **4b** to *N*-unsubstituted tosylate **14b** (74% *vs.* 55%).

Table 2

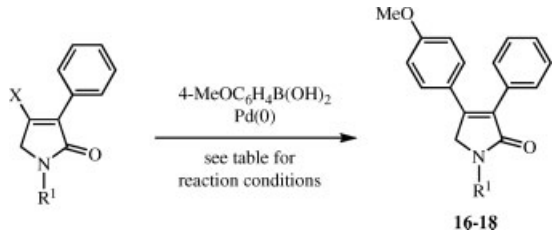


Substrate	R^1	R^2	Product	Yield (%)[a]
4b	Boc	H	**16b**	74
4a	Boc	Ph	**16a**	40
14b	H	H	**18b**	55
14a	H	Ph	**18a**	0

[a] Yields reported are for isolated, chromatographed materials.

Finally, we investigated the reactions of tetramic acid sulfonates with 4-methoxyphenylboronic acid and 2-methoxyphenylboronic acid (Table 3). The results shown in Table 3 describe the effects of sterics of the arylboronic acids on the cross-coupling reactions. With 3-phenyltetramic acid sulfonates **4a** and **7a**, the

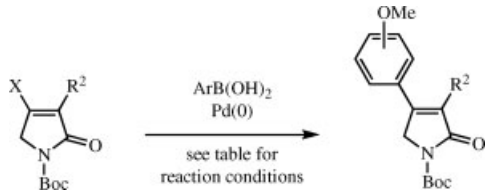
Table 1



Substrate	X	R^1	Methods[a]	Product	Yield (%)[b]
7a	OTf	Boc	A	**16a**	97
3a	OTf	DMB	A	**17a**	95
13a	OTf	H	A	**18a**	62
4a	OTs	Boc	B	**16a**	40
8a	OTs	DMB	B	**17a**	trace
14a	OTs	H	B	**18a**	0

[a] Methods A = $Pd(PPh_3)_4$, Na_2CO_3, THF/H_2O; B = $Pd(dppf)Cl_2$, Cs_2CO_3, THF/H_2O.
[b] Yields reported are for isolated, chromatographed materials.

Table 3



Substrate	X	R^2	Ar	Product	Yield (%)[a]
7a[b]	OTf	Ph	4-$MeOC_6H_4$	**16a**	97
7a[b]	OTf	Ph	2-$MeOC_6H_4$	**19a**	61
4a[c]	OTs	Ph	4-$MeOC_6H_4$	**16a**	40
4a[c]	OTs	Ph	2-$MeOC_6H_4$	**19a**	33
4b[c]	OTs	H	4-$MeOC_6H_4$	**16b**	74
4b[c]	OTs	H	2-$MeOC_6H_4$	**19b**	74

[a] Yields reported are for isolated, chromatographed materials.
[b] Method A.
[c] Method B.

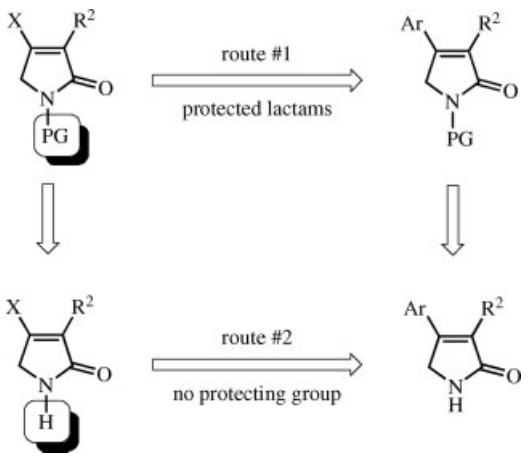
reactions with 4-methoxyphenylboronic acid were higher yielding than the reactions with 2-methoxyphenylboronic acid, although the effect was muted with tosylate **4a**. With the 3-unsubstituted tetramic acid tosylate **4b**, no difference in yield was observed; consequently, the steric effect appears to arise from the vicinal phenyl group (R^2 = Ph) and not from the steric differences of the arylboronic acids.

In conclusion, the Suzuki–Miyaura cross-coupling of tetramic acid sulfonates has proven to be a versatile methodology for the preparation of 3,4-diaryl-3-pyrrolin-2-ones and 4-aryl-3-pyrrolin-2-ones. This synthetic methodology provides facile access to C-4 analogs. The effect that sulfonate ester, sterics, and lactam protection has on the cross-coupling reaction was studied systematically. In all cases, triflates were better cross-coupling partners than the corresponding tosylates. The reactions still proceeded with vicinal phenyl groups, although the yield was partially diminished. We were pleased to find that tetramic acid triflates (and to a lesser extent tetramic acid tosylates) lacking a lactam protecting group proved to be competent substrates [26]. The latter result has the potential to improve the step economy [27] associated with preparing analogs *via* Suzuki–Miyaura cross-coupling reactions of lactams. Each analog can be prepared in one step using *N*-unsubstituted lactam (route #2), while two steps per analog are required with the corresponding *N*-substituted lactam (route #1) (Scheme 4).

EXPERIMENTAL

General remarks. All reactions were performed under a positive argon atmosphere with magnetic stirring unless otherwise noted. Tetrahydrofuran (THF) and CH_2Cl_2 were purified by passage through a column of alumina using a PureSolv 400 solvent purification system. Et_3N was distilled fresh from calcium hydride immediately before use. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. Petroleum ether (PE) refers to the fraction with boiling point 35–60°C. 4-Methoxyphenylboronic acid and 2-methoxyphenylboronic acid were purchased from Aldrich® and used as provided. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in parts per million (δ) using the solvents residual proton or carbon signal ($CDCl_3$: δH 7.24 ppm, δC 77.3 ppm; d_6-DMSO: δH 2.50 ppm, δC 39.5 ppm) as an internal reference. Flash chromatography was performed with silica gel (230–400 mesh), and thin-layer chromatography (TLC) was performed with glass-backed silica gel plates and visualized with UV (254 nm). IR spectra were measured using a Perkin–Elmer Spectrum 100 with ATR sampler (attenuated total reflectance). Known tetramic acid derivatives **3a** [11a], **4b** [11b], and **15**

Scheme 4



[11a] were prepared using our previously published procedures.

Ethyl 2-(2′-phenylacetamido)acetate (10) [23]. A modification of a known procedure to the corresponding methyl ester was followed [28]. To a 0°C stirred solution of glycine ethyl ester hydrochloride (**9**) (10.0 g, 104 mmol) in CH_2Cl_2 (155 mL) was added ice-cooled, neat Et_3N (21.0 g, 28.9 mL, 208 mmol) followed by a solution of phenylacetyl chloride (16.1 g, 13.8 mL, 104 mmol) in CH_2Cl_2 (45 mL) dropwise *via* addition funnel. The cloudy yellow reaction mixture was stirred at 0°C for 2 h and then at rt for 2 h. The organic layer was then washed with H_2O (250 mL), brine (250 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude yellow oil that solidified on standing. Trituration (ether) gave the known titled compound **10** as a yellow amorphous solid (15.6 g, 70.5 mmol, 68% yield): mp 77–79°C (lit. [23b] mp 79–82°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.38 (m, 5H), 5.91 (br s, 1H), 4.15 (q, 3H, J = 7.1 Hz), 3.97 (d, 2H, J = 5.1 Hz), 3.61 (s, 2H), 1.22 (t, 4H, J = 3.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 170.0, 134.7, 129.7, 129.3, 127.7, 61.8, 43.7, 41.7, 14.4 ppm.

Ethyl 2-(*N*-(*tert*-butoxycarbonyl)-2′-phenylacetamido)-acetate (11). To a rt stirred solution of **10** (15.6 g, 70.6 mmol) in CH_3CN (170 mL) was added DMAP (0.862 g, 7.06 mmol) followed by a solution of Boc_2O (16.9 g, 79.0 mmol) in CH_3CN (80 mL). The brown reaction mixture was stirred at rt for 3 h. The solvent was then concentrated *in vacuo* to give a brown oil that was taken up in ether (50 mL) and washed with an aqueous solution of HCl (1*M*, 40 mL), brine (40 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the title compound **11** as a brown oil, which was used directly without further purification (21.0 g, 65.3 mmol, 93% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.29 (m, 5H), 4.43 (s, 2H), 4.28 (s, 2H), 4.16 (q, 2H, J = 7.2 Hz), 1.46 (s, 9H), 1.24 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 169.2, 152.4, 135.1, 129.9, 128.6, 127.1, 84.3, 61.5, 45.9, 44.4, 28.1, 14.5 ppm.

***tert*-Butyl 2,5-dihydro-4-hydroxy-2-oxo-3-phenyl-1*H*-pyrrole-1-carboxylate (12).** To a 0°C stirred solution of **11** (15.1 g, 47.1 mmol) in THF (200 mL) was added sodium *tert*-butoxide (5.43 g, 47.1 mmol). The cloudy rust-colored reaction mixture was stirred at 0°C for 2 h and then at rt overnight. An aqueous solution of $KHSO_4$ (12.8 g, 94.0 mmol in 200 mL H_2O) was added to the reaction mixture and allowed to stir for 20 min. The THF was then removed *in vacuo*, and the remaining aqueous layer was extracted with ethyl acetate (EtOAc) (3 × 80 mL). The combined organic layers were then washed with brine (200 mL) and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude yellow solid. Trituration (EtOAc) gave the titled compound **12** as white crystals (7.04 g, 25.6 mmol, 55% yield): mp 134–135°C; IR (ATR, neat) 3141, 1745, 1718, 1663, 1639, 1408, 1350, 1313, 1257, 1155, 1103, 1073, 980, 898, 851, 780, 754, 742, 721, 694, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.39 (br s, 1H), 7.84 (d, 2H, J = 7.2 Hz), 7.35 (t, 2H, J = 7.5 Hz), 7.20 (t, 1H, J = 7.5), 4.27 (s, 2H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 168.0, 149.0, 131.1, 127.9, 127.0, 126.2, 103.5, 81.1, 47.9, 27.8 ppm; *Anal.* calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.23; H, 6.22; N, 5.00.

***tert*-Butyl 2,5-dihydro-2-oxo-3-phenyl-4-(trifluoromethylsulfonoxy)-1*H*-pyrrole-1-carboxylate (7a).** To a −15°C stirred solution of **12** (1.21 g, 4.65 mmol) in CH_2Cl_2 (30 mL) was added neat Et_3N (0.626 g, 0.860 mL, 6.18 mmol) followed by neat trifluoromethanesulfonic anhydride (Tf_2O; 1.44 g, 0.860 mL, 5.11 mmol) dropwise *via* syringe. The reaction mixture was stirred at −15°C for 2.5 h at which point TLC showed complete conversion of the starting material **12**. The reaction mixture first turned green on the addition of Tf_2O, and then turned into a clear yellow solution after 5 min. The reaction mixture was poured onto an aqueous solution of $KHSO_4$ (1.27 g, 9.33 mmol in 75 mL H_2O) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with an aqueous solution of sodium bicarbonate (1% *w*/*v*, 100 mL), brine (100 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude yellow solid (1.36 g). Purification by flash column chromatography (gradient: 1:15 to 1:11 EtOAc/PE) gave the titled compound **7a** as an analytically pure yellow solid (1.07 g, 2.63 mmol, 57% yield): mp 94–96°C; R_f = 0.34 (1:8 EtOAc/PE); IR (ATR, neat) 2980, 1772, 1693, 1449, 1424, 1371, 1328, 1311, 1293, 1247, 1223, 1211, 1151, 1133, 1096, 969, 922, 902, 847, 820, 783, 764, 735, 696, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.65 (m, 2H), 7.41–7.44 (m, 3H), 4.59 (s, 2H), 1.57 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6, 154.9, 149.2, 130.2, 129.1, 129.0, 126.2, 124.6, 118.5 (q, J = 320 Hz), 84.6, 47.8, 28.3 ppm; *Anal.* calcd for $C_{16}H_{16}F_3NO_6S$: C, 47.17; H, 3.96; N, 3.44. Found: C, 47.13; H, 3.89; N, 3.39.

***tert*-Butyl 2,5-dihydro-2-oxo-3-phenyl-4-(tosyloxy)-1*H*-pyrrole-1-carboxylate (4a).** To a rt stirred solution of **12** (1.00 g, 3.65 mmol) in CH_2Cl_2 (40 mL) was added TsCl (0.730 g, 3.83 mmol) followed by neat Et_3N (0.443 g, 0.608 mL, 4.38 mmol) dropwise *via* syringe. The reaction mixture was stirred at rt for 1 h at which point TLC showed complete conversion of the starting material **12**. The reaction mixture was poured onto an aqueous solution of $KHSO_4$ (0.992 g, 7.30 mmol in 50 mL H_2O) and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with an aqueous solution of sodium bicarbonate (1% *w*/*v*, 150 mL), brine (150 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the titled compound **4a** as a yellow amorphous solid (1.44 g, 3.35 mmol, 92% yield). Recrystallization (CH_2Cl_2) gave the analytical sample as yellow crystals: mp 137–140°C; R_f = 0.76 (1:2 EtOAc/PE); IR (ATR, neat) 1770, 1450, 1377, 1335, 1314, 1287, 1192, 1159, 1091, 977, 898, 781, 761, 697, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, 2H, J = 8.4 Hz), 7.35–7.39 (m, 2H), 7.21–7.25 (m, 3H), 7.11 (d, 2H, J = 9.0 Hz), 4.58 (s, 1H), 2.35 (s, 3H), 1.57 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 156.6, 149.0, 147.5, 131.1, 129.9, 128.7, 128.6, 128.2, 128.0, 127.0, 122.5, 83.7, 48.2, 28.1, 21.7 ppm; *Anal.* calcd for $C_{22}H_{23}NO_6S$: C, 61.52; H, 5.40; N, 3.26. Found: C, 61.13; H, 5.46; N, 3.31.

2,5-Dihydro-2-oxo-3-phenyl-4-(trifluoromethylsulfonoxy)-1*H*-pyrrole (13a). To a rt stirred solution of **7a** (1.50 g, 3.68 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction mixture was stirred at rt for 5 min at which point TLC showed complete conversion of the starting material **7a**. Removal of the solvent *in vacuo* gave a crude brown oil that was taken up in $CHCl_3$ (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL) and the combined organic layers were then washed with brine (50 mL) and

dried over sodium sulfate. Removal of the solvent *in vacuo* gave the titled compound **13a** as a yellow amorphous solid (1.10 g, 3.58 mmol, 97% yield). Recrystallization (EtOH) gave the analytical sample as yellow crystals: mp 117–119°C; R_f = 0.33 (1:2 EtOAc/PE); IR (ATR, neat) 3072, 1699, 1420, 1333, 1211, 1170, 1134, 1025, 958, 919, 825, 781, 766, 735, 694, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 7.61–7.64 (m, 2H), 7.46–7.49 (m, 3H), 4.36 (d, 2H, J = 1.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 155.6, 129.3, 128.5, 128.4, 127.2, 123.3, 117.7 (q, J = 320 Hz), 44.5 ppm; *Anal.* calcd for $C_{11}H_8F_3NO_4S$: C, 43.00; H, 2.62; N, 4.56. Found: C, 42.91; H, 2.59; N, 4.58.

2,5-Dihydro-2-oxo-3-phenyl-4-(tosyloxy)-1*H*-pyrrole (14a). To a rt stirred solution of **4a** (1.00 g, 2.33 mmol) in CH_2Cl_2 (20 mL) was added TFA (20 mL). The reaction mixture was stirred at rt for 5 min at which point TLC showed complete conversion of the starting material **4a**. Removal of the solvent *in vacuo* gave a crude brown oil that was taken up in $CHCl_3$ (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic layers were then washed with a saturated aqueous solution of sodium bicarbonate (200 mL), brine (200 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave titled compound **14a** as a yellow amorphous solid (0.750 g, 2.28 mmol, 98% yield). Recrystallization (CH_2Cl_2) gave the analytical sample as light yellow crystals: mp 159–161°C; R_f = 0.21 (1:1 EtOAc/PE); IR (ATR, neat) 3071, 1686, 1593, 1497, 1451, 1360, 1306, 1236, 1204, 1182, 1172, 1088, 1039, 960, 813, 786, 735, 703, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.73–7.76 (m, 2H), 7.28–7.37 (m, 7H), 4.20 (d, 2H, J = 0.9 Hz), 2.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 156.6, 146.6, 130.5, 130.2, 128.2, 128.1, 128.0, 127.9, 121.5, 44.9, 21.2 ppm; *Anal.* calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 62.00; H, 4.64; N, 4.29.

2,5-Dihydro-1-(3′,4′-dimethoxybenzyl)-2-oxo-3-phenyl-4-(tosyloxy)-1*H*-pyrrole (8a). To a rt stirred solution of known tetramic acid **15** [2] (2.00 g, 6.18 mmol) in CH_2Cl_2 (60 mL) was added TsCl (1.23 g, 6.46 mmol) followed by neat Et_3N (0.748 g, 1.028 mL, 7.39 mmol) dropwise *via* syringe. The reaction mixture was stirred at rt for 2 h at which point TLC showed complete conversion of the starting material **15**. The reaction mixture was poured onto an aqueous solution of $KHSO_4$ (1.99 g, 14.6 mmol in 75 mL H_2O) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with an aqueous solution of sodium bicarbonate (1% *w/v*, 150 mL), brine (150 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude clear oil (2.79 g) that was purified by flash column chromatography (gradient: 1:5 to 1:1 EtOAc/PE). Removal of the solvent *in vacuo* gave the titled compound **8a** as a clear oil. Trituration (MeOH) gave the analytical sample as a white solid (1.94 g, 4.05 mmol, 66% yield): mp 110–112°C; R_f = 0.17 (1:2 EtOAc/PE); IR (ATR, neat) 1688, 1593, 1517, 1447, 1405, 1356, 1338, 1296, 1280, 1263, 1356, 1338, 1296, 1280, 1263, 1236, 1205, 1160, 1136, 1090, 1022, 973, 956, 900, 814, 787, 766, 741, 706, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, 2H, J = 8.1 Hz), 7.43–7.46 (m, 2H), 7.20–7.22 (m, 3H), 7.05 (d, 2H, J = 8.7 Hz), 6.79 (d, 3H, J = 12 Hz), 4.59 (s, 2H), 4.12 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 154.8, 149.6, 149.0, 146.5, 131.4, 130.0, 129.4, 128.8, 128.6, 128.4, 128.2, 122.5, 120.9, 111.5, 111.4, 56.2, 49.4, 46.1, 21.9 ppm; *Anal.* calcd for $C_{26}H_{25}NO_6S$: C, 65.12; H, 5.25; N, 2.92. Found: C, 65.05; H, 5.37; N, 2.92.

2,5-Dihydro-2-oxo-4-(tosyloxy)-1*H*-pyrrole (14b). To a 0°C stirred solution of known tosylate **4b** [11b] (0.600 g, 1.70 mmol) in CH_2Cl_2 (8.6 mL) was added TFA (8.6 mL) dropwise *via* syringe. The reaction mixture was stirred for 0.5 h. Removal of the solvent *in vacuo* gave a crude product that was taken up in $CHCl_3$ (25 mL) and washed with an aqueous solution of sodium bicarbonate (5% *w/v*, 2 × 25 mL), brine (25 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave the titled compound **14b** as a white amorphous solid (0.355 g, 1.40 mmol, 83% yield): mp 151–153°C; IR (ATR, neat) 3102, 1693, 1631, 1596, 1386, 1360, 1325, 1216, 1196, 1184, 1161, 1092, 980, 921, 877, 818, 803, 782, 704, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (s, 1H), 7.96 (d, 2H, J = 8.4 Hz), 7.54 (d, 2H, J = 8.1 Hz), 5.62 (d, 1H, J = 1.5 Hz), 3.93 (t, 2H, J = 1.2 Hz), 2.45 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 163.3, 146.9, 130.6, 130.4, 128.5, 107.4, 46.2, 21.2 ppm; *Anal.* calcd for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 52.10; H, 4.30; N, 5.47; S, 12.71.

General procedures for Suzuki–Miyaura reactions

Method A (tetramic acid triflates). To a rt stirred solution of tetramic acid triflate (1.00 mmol) in THF (10 mL) was added an arylboronic acid (1.50 mmol) and was allowed to dissolve completely. To this solution was added $Pd(PPh_3)_4$ (0.050 mmol) followed by an aqueous solution of sodium carbonate (2.2 mmol in 1 mL H_2O). The reaction mixture was stirred at rt for 40 min and then heated to reflux until TLC showed complete conversion of the starting triflate (typically 1–3 h). The reaction mixture was then filtered through a short plug of celite with the aid of EtOAc. Removal of the solvent *in vacuo* gave a crude solid that was purified by flash column chromatography (gradient: 1:4 to 1:1 EtOAc/PE).

Method B (tetramic acid tosylates). To a rt stirred solution of tetramic acid tosylate (1.00 mmol) in THF (10 mL) was added an arylboronic acid (1.50 mmol) and was allowed to dissolve completely. To this solution was added $Pd(dppf)Cl_2$ (0.050 mmol) followed by a solution of an aqueous solution of cesium carbonate (3.00 mmol, 1 mL H_2O). The reaction mixture was stirred at rt for 40 min and then heated to reflux until TLC showed complete conversion of the starting material (typically 12–20 h). The reaction mixture was then filtered through a short plug of celite with the aid of EtOAc. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (50 mL), brine (50 mL), and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a crude oil that was purified by flash column chromatography (gradient: CH_2Cl_2 to 8:92 EtOAc/CH_2Cl_2).

***tert*-Butyl 2,5-dihydro-4-(4′-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole-1-carboxylate (16a).** Using triflate **7a**, Method **A** was followed and gave the titled compound **16a** as a light yellow amorphous solid (97% yield). Recrystallization (EtOAc) gave the analytical sample as white crystals: mp 177–179°C; R_f = 0.60 (1:2 EtOAc/PE); IR (ATR, neat) 1763, 1686, 1604, 1516, 1450, 1366, 1348, 1313, 1298, 1257, 1160, 1123, 1097, 1027, 926, 912, 851, 835, 787, 743, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.34 (m, 5H), 7.26 (d, 2H,

J = 7.5 Hz), 6.79 (d, 2H, J = 9.0 Hz), 4.64 (s, 2H), 3.79 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 161.2, 150.5, 149.3, 131.8, 130.7, 129.9, 129.7, 128.8, 128.6, 124.7, 114.4, 83.3, 55.6, 50.9, 28.4 ppm; *Anal*. calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.10; H, 6.38; N, 3.87.

Using tosylate **4a**, Method **B** was followed and gave the titled compound **16a** as a light yellow amorphous solid (40% yield) which gave spectral data consistent with the material prepared from triflate **7a**.

2,5-Dihydro-1-(3′,4′-dimethoxybenzyl)-4-(4″-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole (17a). Using triflate **3a** [11a], Method **A** was followed and gave the titled compound **17a** as a yellow amorphous solid as reported previously [11a] (95% yield).

Using tosylate **8a**, Method **B** was followed in an attempt to obtain the titled compound **17a**; however, only a trace amount of product was formed as seen by TLC. Flash column chromatography gave only starting material **3a**.

2,5-Dihydro-4-(4′-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole (18a). Using triflate **13a**, Method **A** was followed and gave the titled compound **18a** as a white amorphous solid (62% yield): mp 169–174°C (lit. [11a] mp 193–196°C); R_f = 0.28 (1:1 EtOAc/PE); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H), 7.29–7.37 (m, 3H) 7.24–7.28 (m, 4H) 6.87 (d, 2H, J = 8.7 Hz), 4.33 (s, 2H), 3.74 (s, 3H) ppm. The physical properties and spectral data for 18a were consistent to that reported previously [11a].

Using tosylate **14a**, Method **B** was followed in an attempt to obtain **18a**; however, spectroscopic and TLC assessment of the crude material obtained on work-up failed to reveal even reveal a trace of **18a**.

***tert*-Butyl 2,5-dihydro-4-(4′-methoxyphenyl)-2-oxo-1*H*-pyrrole-1-carboxylate (16b).** Using tosylate **4b** [11b], Method **B** was followed and gave the titled compound **16b** as a tan amorphous solid (74% yield): mp 151–154°C (lit. [11b] mp 158–160°C); R_f = 0.31 (1:2 EtOAc/PE); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, 2H, J = 9 Hz), 6.92 (d, 2H, J = 8.7 Hz), 6.24 (t, 1H, J = 1.2 Hz), 4.62 (d, 2H, J = 1.5 Hz), 3.82 (s, 3H), 1.55 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 162.2, 156.0, 150.0, 128.1, 123.7, 117.6, 114.8, 83.1, 55.7, 51.2, 28.4 ppm. The physical properties and spectral data for **16b** were consistent to that reported previously [11b].

2,5-Dihydro-4-(4′-methoxyphenyl)-2-oxo-1H-pyrrole (18b). Using tosylate **14b**, Method **B** was followed and gave the titled compound **18b** as a tan amorphous solid (55% yield): mp 185–188°C (lit. [11b] mp 198–199°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H), 7.61 (q, 2H, J = 4.5 Hz), 6.99 (d, 2H, J = 8.7 Hz), 6.38 (d, 1H, J = 1.2 Hz), 6.33 (d, 2H, J = 0.9 Hz), 3.80 (s, 3H) ppm. The physical properties and spectral data for **18b** were consistent to that reported previously [11b].

***tert*-Butyl 2,5-dihydro-4-(2′-methoxyphenyl)-2-oxo-3-phenyl-1*H*-pyrrole-1-carboxylate (19a).** Using triflate **7a**, Method **A** was followed and gave the titled compound **19a** as a yellow oil which partially solidified (61% yield). Crystallization (EtOH) gave the analytical sample as yellow crystals: mp 122–126°C; R_f = 0.44 (1:4 EtOAc/PE); IR (ATR, neat) 2967, 1759, 1680, 1596, 1470, 1350, 1292, 1257, 1152, 1100, 1014, 912, 786, 756, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.31 (m, 3H), 7.21–7.23 (m, 2H), 7.00–7.03 (m, 1H), 6.82–6.90 (m, 2H), 4.65 (s, 2H), 3.65 (s, 3H), 1.57 (s 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 157.2, 150.4, 149.8, 133.2, 131.6, 131.1, 130.5, 129.4, 128.3, 128.2, 122.1, 122.0, 111.6, 83.1, 55.5, 52.1, 28.5 ppm; *Anal*. calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.03; H, 6.46; N, 3.81.

Using tosylate **4a**, Method **B** was followed and gave the titled compound **19a** as a yellow oil (33% yield) that gave spectral data consistent with the material prepared from **7a**.

2,5-Dihydro-4-(2′-methoxyphenyl)-2-oxo-1*H*-pyrrole-1-carboxylate (19b). Using tosylate **4b** [11b], Method **B** was followed and gave the titled compound **19b** as a brown amorphous solid (74% yield). Trituration (EtOH) gave the analytical sample as white crystals: mp 127–128°C; R_f = 0.33 (5:95 EtOAc/CH_2Cl_2); IR (ATR, neat) 1756, 1678, 1606, 1577, 1501, 1455, 1362, 1333, 1293, 1251, 1156, 1077, 1015, 876, 852, 789, 759, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.41 (m, 2H), 6.95–6.99 (m, 2H), 6.65 (s, 1H), 4.71 (d, 2H, J = 1.5 Hz), 3.89 (s, 3H), 1.56 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 158.9, 153.1, 150.0, 132.5, 128.4, 123.0, 121.0, 120.1, 111.8, 83.0, 55.7, 52.8 ppm; *Anal*. calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.33; H, 6.67; N, 4.92.

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