N-Acylsuccinimides: Twisted-Controlled, Acyl Transfer Reagents in Suzuki-Miyaura Cross-Coupling Osumi et al.

N-Acylsuccinimides: Twist-Controlled, Acyl-Transfer Reagents in Suzuki-Miyaura Cross-Coupling by N–C Amide Bond Activation

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List of Known Compounds/General Methods

All starting materials reported in the manuscript have been prepared according to the method reported previously.^{1,2} All experiments involving palladium were performed using standard Schlenk techniques under argon atmosphere unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All solvents were deoxygenated prior to use. All other chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon (three cycles). All products were identified using ¹H NMR analysis and comparison with authentic samples. GC and/or GC/MS analysis was used for volatile products. All yields refer to yields determined by ¹H NMR and/or GC or GC/MS using an internal standard (optimization) and isolated yields (preparative runs) unless stated otherwise. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on Bruker spectrometers at 500 (¹H NMR) and 125 MHz (¹³C NMR). All shifts are reported in parts per million (ppm) relative to residual CHCl₃ peak (7.27 and 77.2 ppm, ¹H NMR and ¹³C NMR, respectively). All coupling constants (J) are reported in hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet. GC-MS chromatography was performed using Agilent HP6890 GC System and Agilent 5973A inert XL EI/CI MSD using helium as the carrier gas at a flow rate of 1 mL/min and an initial oven temperature of 50 °C. The injector temperature was 250 °C. The detector temperature was 250 °C. For runs with the initial oven temperature of 50 °C, temperature was increased with a 10 °C/min ramp after 50 °C hold for 3 min to a final temperature of 220 °C, then hold at 220 °C for 15 min (splitless mode of injection, total run time of 22.0 min). Highresolution mass spectra (HRMS) were measured on a 7T Bruker Daltonics FT-MS instrument (for HRMS). Melting point was measured on MeltEMP (laboratory devices). All flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on glass plates coated with silica gel 60 F254, 0.2 mm thickness. The plates were visualized using a 254 nm ultraviolet lamp or aqueous potassium permanganate solutions. ¹H NMR and ¹³C NMR data are given for all compounds in the Supplementary Information. ¹H NMR, ¹³C NMR and HRMS data are reported for all new compounds. All compounds reported in this manuscript have been previously reported, unless stated otherwise. Spectroscopic data matched literature values.

Experimental Procedures and Characterization Data

General Procedure for Amide Synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with succinimide (typically, 5.0 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (typically, 0.005 equiv), triethylamine (typically, 2.0 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated. The crude product was purified by recrystallization (toluene) to afford analytically pure product.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), $Pd(OAc)_2$ (typically, 3 mol%), PCy_3HBF_4 (typically, 12 mol%) and Na_2CO_3 (typically, 2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

Representative Procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with 1-benzoylpyrrolidine-2,5-dione (neat, 40.7 mg, 0.20 mmol), *p*-tolylboronic acid (2.0 equiv), $Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%) and Na_2CO_3 (2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for 15 h at 120 °C. After the indicated time, the reaction mixture was cooled down to

room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. A sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product. Yield 97% (38.1 mg, 0.194 mmol). White solid. Characterization data are included in the section below.

Characterization Data for Starting Materials

Note: All starting materials have been prepared according to the previously published procedure.^{1,2} The yields have not been optimized.



1-Benzoylpyrrolidine-2,5-dione (1a). 1a is commercially available [CAS: 6343-27-7]. White solid. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 7.88-7.87 (d, J = 7.5 Hz, 2 H), 7.71-7.68 (t, J = 7.5 Hz, 1 H), 7.54-7.51 (t, J = 7.8 Hz, 2 H), 2.96 (s, 4 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 174.56, 167.64, 135.16, 131.41, 130.54, 128.98, 29.08.



1b

1-(4-Methylbenzoyl)pyrrolidine-2,5-dione (1b).¹ Yield: 85% (0.923 g). White solid. <u>¹H NMR</u> (500 MHz, CDCl₃) δ 7.78-7.76 (d, J = 8.3 Hz, 2 H), 7.33-7.31 (d, J = 8.0 Hz, 2 H), 2.95 (s, 4 H), 2.46 (s, 3 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 174.70, 167.36, 146.67, 130.74, 129.75, 128.75, 29.08, 21.95.



1-(4-Methoxybenzoyl)pyrrolidine-2,5-dione (1c).¹ Yield: 74% (0.863 g). White solid. <u>¹H</u> <u>NMR (500 MHz, CDCl₃)</u> δ 7.86-7.85 (d, J = 9.0 Hz, 2 H), 7.00-6.98 (d, J = 9.0 Hz, 2 H), 3.92 (s, 3 H), 2.95 (s, 4 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 174.83, 166.47, 165.38, 133.27, 123.85, 114.40, 55.72, 29.10.



1-(4-(Trifluoromethyl)benzoyl)pyrrolidine-2,5-dione (1d).¹ Yield: 71% (0.963 g). White solid. ¹<u>H NMR (500 MHz, CDCl₃)</u> δ 7.97-7.95 (d, J = 8.2 Hz, 2 H), 7.79-7.77 (d, J = 8.3 Hz, 2 H), 2.98 (s, 4 H). ¹³<u>C NMR (125 MHz, CDCl₃)</u> δ 174.23, 166.66, 135.99 (q, $J^2 = 32.8$ Hz), 134.56, 130.66, 125.97 (q, $J^3 = 3.7$ Hz), 123.26 (q, $J^1 = 271.3$ Hz), 29.03. ¹⁹<u>F NMR (471 MHz, CDCl₃)</u> δ -63.39.



1-(2-Methylbenzoyl)pyrrolidine-2,5-dione (1e).¹ Yield: 75% (0.815 g). White solid. <u>¹H NMR</u> (500 MHz, CDCl₃) δ 7.52-7.49 (t, J = 7.9 Hz, 2 H), 7.36-7.34 (d, J = 7.6 Hz, 1 H), 7.31-7.28 (t, J = 7.7 Hz, 1 H), 2.91 (s, 4 H), 2.62 (s, 3 H). <u>¹³C NMR (125 MHz, CDCl_3)</u> δ 174.44, 167.64, 141.21, 133.62, 132.27, 131.20, 130.62, 126.03, 28.93, 21.18.



1-(4-Acetylbenzoyl)pyrrolidine-2,5-dione (1f). Yield: 49% (0.601 g). <u>New compound.</u> White solid. <u>Mp</u> = 100-102 °C. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 8.07-8.05 (d, *J* = 8.2 Hz, 2 H), 7.94-7.92 (d, *J* = 8.3 Hz, 2 H), 2.97 (s, 4 H), 2.67 (s, 3 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 197.07, 174.35, 167.01, 141.41, 134.91, 130.57, 128.59, 29.05, 26.95. <u>HRMS</u> calcd for C₁₃H₁₁NO₄NK (M⁺ + K) 284.0320, found 284.0310.



1-(4-(Methoxycarbonyl)benzoyl)pyrrolidine-2,5-dione (1g). Yield: 70% (0.915 g). <u>New</u> <u>compound.</u> White solid. <u>Mp</u> = 139-141 °C. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 8.18-8.16 (d, *J* = 8.5 Hz, 2 H), 7.92-7.90 (d, *J* = 8.5 Hz, 2 H), 3.98 (s, 3 H), 2.98 (s, 4 H). <u>¹³C NMR (125 MHz, CDCl_3)</u> δ 174.30, 167.06, 165.76, 135.49, 134.93, 130.27, 129.99, 52.67, 29.05. <u>HRMS</u> calcd for C₁₃H₁₁NO₅Na (M⁺ + Na) 284.0529, found 284.0531.



1h

1-(Thiophene-2-carbonyl)pyrrolidine-2,5-dione (1h). Yield: 89% (0.931 g). <u>New compound.</u> White solid. <u>Mp</u> = 78-80 °C. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 7.85-7.84 (d, *J* = 4.9 Hz, 1 H), 7.73-7.72 (d, *J* = 3.9 Hz, 1 H), 7.20-7.18 (t, *J* = 4.1 Hz, 1 H), 2.94 (s, 4 H). <u>¹³C NMR (125 MHz,</u> <u>CDCl₃)</u> δ 174.36, 160.66, 137.62, 136.86, 136.66, 128.72, 29.08. <u>HRMS</u> calcd for C₉H₇NO₃S (M⁺) 209.0141, found 209.0145.



1-(Cyclohexanecarbonyl)pyrrolidine-2,5-dione (1i). Yield: 64% (0.670 g). <u>New compound.</u> White solid. <u>Mp</u> = 82-84 °C. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 3.14-3.08 (m, 1 H), 2.81 (s, 4 H), 1.94-1.91 (m, 2 H), 1.82-1.79 (m, 2 H), 1.69-1.67 (m, 1 H), 1.53-1.45 (m, 2 H), 1.38-1.22 (m, 3 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 176.12, 174.42, 45.99, 28.61, 28.19, 25.63, 25.22. <u>HRMS</u> calcd for C₁₁H₁₅NO₃Na (M⁺ + Na) 232.0944, found 232.0926.

Suzuki-Miyaura Coupling of Amides: Variation of Boronic Acids

p-Tolylboronic acid (2a, Table 2, Entry 1)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), *p*-tolylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 97% yield (38.1 mg). White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.82-7.80 (d, *J* = 8.1 Hz, 2 H), 7.76-7.74 (d, *J* = 8.0 Hz, 2 H), 7.62-7.59 (t, *J* = 7.5 Hz, 1 H), 7.51-7.48 (t, *J* = 7.6 Hz, 2 H), 7.32-7.28 (d, *J* = 7.9 Hz, 2 H), 2.47 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 196.53, 143.26, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

p-Methoxyphenylboronic acid (2b, Table 2, Entry 2)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), *p*-methoxyphenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 93% yield (39.5 mg). White solid. <u>¹H NMR (500 MHz,</u> <u>CDCl₃)</u> δ 7.87-7.85 (d, *J* = 8.7 Hz, 2 H), 7.79-7.77 (d, *J* = 8.2 Hz, 2 H), 7.61-7.58 (t, *J* = 6.8 Hz, 1 H), 7.51-7.48 (t, *J* = 7.6 Hz, 2 H), 7.00-6.98 (d, *J* = 8.7 Hz, 2 H), 3.92 (s, 3 H). <u>¹³C NMR (125</u> <u>MHz, CDCl₃)</u> δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

p-(Trifluoromethyl)phenylboronic acid (2c, Table 2, Entry 3)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), *p*-(trifluoromethyl)phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 84% yield (42.1 mg). White solid. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 7.93-7.91 (d, *J* = 8.0 Hz, 2 H), 7.84-7.82 (d, *J* = 8.2 Hz, 2 H), 7.79-7.77 (d, *J* = 8.1 Hz, 2 H), 7.67-7.64 (t, *J* = 7.6 Hz, 1 H), 7.55-7.52 (t, *J* = 7.7 Hz, 2 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 195.55, 140.74, 136.75, 133.74 (q, *J*² = 32.5 Hz), 133.11, 130.15, 130.12, 128.55, 125.37 (q, *J*³ = 3.7 Hz), 123.69 (q, *J*^{*l*} = 270.9 Hz). <u>¹⁹F NMR (471 MHz, CDCl₃)</u> δ -63.00.

o-Tolylboronic acid (2d, Table 2, Entry 4)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), *o*-tolylboronic acid (3.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (4.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 65% yield (25.5 mg). White solid. ¹<u>H NMR (500 MHz, CDCl₃)</u> δ 7.84-7.82 (d, *J* = 8.3 Hz, 2 H), 7.62-7.59 (t, *J* = 7.5 Hz, 1H), 7.50-7.47 (t, *J* = 7.9 Hz, 2 H), 7.43-7.40 (t, *J* = 7.5 Hz, 1 H), 7.35-7.31 (t, *J* = 7.8 Hz, 2 H), 7.29-7.26 (t, *J* = 7.5 Hz, 1 H), 2.36 (s, 3 H). ¹³<u>C</u> <u>NMR (125 MHz, CDCl₃)</u> δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

4-Formylphenylboronic acid (2e, Table 2, Entry 5)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), 4-formylphenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 96% yield (40.4 mg). White solid. ¹H NMR (500 MHz, CDCl₃) δ 10.16 (s, 1 H), 8.04-8.02 (d, *J* = 8.3 Hz, 2 H), 7.96-7.95 (d, *J* = 8.2 Hz, 2 H), 7.84-7.83 (d, *J* = 7.1 Hz, 2 H), 7.68-7.65 (t, *J* = 7.5 Hz, 1 H), 7.55-7.52 (t, *J* = 7.9 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 195.85, 191.65, 142.59, 138.49, 136.76, 133.16, 130.35, 130.14, 129.52, 128.56.

3-Acetylphenylboronic acid (2f, Table 2, Entry 6)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), 3-acetylphenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 91% yield (40.8 mg). White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.39 (s, 1 H), 8.21-8.20 (d, *J* = 7.8 Hz, 1 H), 8.02-8.00 (d, *J* = 7.7 Hz, 1 H), 7.83-7.82 (d, *J* = 7.1 Hz, 2 H), 7.66-7.61 (m, 2 H), 7.54-7.51 (t, *J* = 7.8 Hz, 2 H), 2.67 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 197.33, 195.89, 138.09, 137.20, 137.02, 134.27, 132.91, 131.78, 130.06, 129.72, 128.77, 128.53, 26.78.

2-Formylphenylboronic acid (2g, Table 2, Entry 7)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), 2-formylphenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 140 °C, afforded after work-up and chromatography the title compound in 95% yield (40.0 mg). White solid. ¹H NMR (500 MHz, CDCl₃) δ 10.05 (s, 1 H), 8.07-8.05 (m, 1 H), 7.83-7.82 (d, *J* = 7.2 Hz, 2 H), 7.72-7.71 (t, *J* = 3.4 Hz, 2 H), 7.65-7.62 (t, *J* = 7.4 Hz, 1 H), 7.54-7.53 (m, 1 H), 7.51-7.48 (t, *J* = 7.9 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 196.53, 190.61, 141.42, 137.08, 135.42, 133.69, 133.36, 130.63, 130.07, 129.98, 128.90, 128.68.

3,5-Difluorophenylboronic acid (2h, Table 2, Entry 8)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), 3,5-difluorophenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 50% yield (21.9 mg). White solid. ¹H NMR (500 MHz, <u>CDCl₃</u>) δ 7.83-7.81 (d, *J* = 7.2 Hz, 2 H), 7.67-7.64 (t, *J* = 7.5 Hz, 1 H), 7.55-7.52 (t, *J* = 7.8 Hz, 2 H), 7.35-7.34 (d, *J* = 5.7 Hz, 2 H), 7.09-7.05 (t, *J* = 8.5 Hz, 1 H). ¹³C NMR (125 MHz, <u>CDCl₃</u>) δ 193.95, 163.70 (d, *J*² = 11.7 Hz), 161.70 (d, *J*³ = 11.6 Hz), 136.40, 133.16, 129.98, 128.59, 112.95 (d, *J*⁴ = 6.4 Hz), 107.72 (d, *J*^l = 25.4 Hz). ¹⁹F NMR (471 MHz, CDCl₃) δ - 108.15.

3-Furanylboronic acid (2i, Table 2, Entry 9)



According to the general procedure, the reaction of 1-benzoylpyrrolidine-2,5-dione (0.20 mmol), 3-furanylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 63% yield (21.7 mg). Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.95 (s, 1 H), 7.89-7.88 (d, *J* = 7.2 Hz, 2 H), 7.63-7.60 (t, *J* = 7.5 Hz, 1 H), 7.54-7.50 (t, *J* = 8.0 Hz, 3 H), 6.94 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 189.46, 148.58, 143.98, 138.85, 132.50, 128.85, 128.57, 126.54, 110.24.

Suzuki-Miyaura Cross-Coupling of Amides: Variation of Amides

1-(4-Methylbenzoyl)pyrrolidine-2,5-dione (1b, Table 3, Entry 1)



According to the general procedure, the reaction of 1-(4-methylbenzoyl)pyrrolidine-2,5-dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 96% yield (37.7 mg). White solid. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 7.82-7.80 (d, *J* = 8.1 Hz, 2 H), 7.76-7.74 (d, *J* = 8.0 Hz, 2 H), 7.62-7.59 (t, *J* = 7.5 Hz, 1 H), 7.51-7.48 (t, *J* = 7.6 Hz, 2 H), 7.32-7.28 (d, *J* = 7.9 Hz, 2 H), 2.47 (s, 3 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 196.53, 143.26, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

1-(4-Methoxybenzoyl)pyrrolidine-2,5-dione (1c, Table 3, Entry 2)



According to the general procedure, the reaction of 1-(4-methoxybenzoyl)pyrrolidine-2,5-dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 89% yield (37.8 mg). White solid. ¹H NMR (500 MHz, <u>CDCl₃</u>) δ 7.87-7.85 (d, *J* = 8.7 Hz, 2 H), 7.79-7.77 (d, *J* = 8.2 Hz, 2 H), 7.61-7.58 (t, *J* = 6.8 Hz, 1 H), 7.51-7.48 (t, *J* = 7.6 Hz, 2 H), 7.00-6.98 (d, *J* = 8.7 Hz, 2 H), 3.92 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

1-(4-(Trifluoromethyl)benzoyl)pyrrolidine-2,5-dione (1d, Table 3, Entry 3)



According to the general procedure, the reaction of 1-(4-(trifluoromethyl)benzoyl)pyrrolidine-2,5-dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 98% yield (49.1 mg). White solid. ¹H NMR (500 <u>MHz, CDCl₃</u>) δ 7.93-7.91 (d, *J* = 8.0 Hz, 2 H), 7.84-7.82 (d, *J* = 8.2 Hz, 2 H), 7.79-7.77 (d, *J* = 8.1 Hz, 2 H), 7.67-7.64 (t, *J* = 7.6 Hz, 1 H), 7.55-7.52 (t, *J* = 7.7 Hz, 2 H). ¹³C NMR (125 MHz, <u>CDCl₃</u>) δ 195.55, 140.74, 136.75, 133.74 (q, *J*² = 32.5 Hz), 133.11, 130.15, 130.12, 128.55, 125.37 (q, *J*³ = 3.7 Hz), 123.69 (q, *J*^{*l*} = 270.9 Hz). ¹⁹F NMR (471 MHz, CDCl₃) δ -63.00.

1-(2-Methylbenzoyl)pyrrolidine-2,5-dione (1e, Table 3, Entry 4)



According to the general procedure, the reaction of 1-(2-methylbenzoyl)pyrrolidine-2,5-dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 73% yield (28.7 mg). White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.84-7.82 (d, *J* = 8.3 Hz, 2 H), 7.62-7.59 (t, *J* = 7.5 Hz, 1H), 7.50-7.47 (t, *J* = 7.9 Hz, 2 H), 7.43-7.40 (t, *J* = 7.5 Hz, 1 H), 7.35-7.31 (t, *J* = 7.8 Hz, 2 H), 7.29-7.26 (t, *J* = 7.5 Hz, 1 H), 2.36 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

1-(4-Acetylbenzoyl)pyrrolidine-2,5-dione (1f, Table 3, Entry 5)



According to the general procedure, the reaction of 1-(4-acetylbenzoyl)pyrrolidine-2,5-dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 66% yield (29.6 mg). White solid. ¹H NMR (500 MHz, <u>CDCl₃</u>) δ 8.09-8.08 (d, *J* = 8.3 Hz, 2 H), 7.90-7.88 (d, *J* = 8.3 Hz, 2 H), 7.84-7.82 (d, *J* = 7.1 Hz, 2 H), 7.66-7.63 (t, *J* = 7.5 Hz, 1 H), 7.55-7.51 (t, *J* = 7.8 Hz, 2 H), 2.70 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 197.54, 195.98, 141.35, 139.58, 136.93, 133.01, 130.12, 130.07, 128.50, 128.18, 26.92.

1-(4-(Methoxycarbonyl)benzoyl)pyrrolidine-2,5-dione (1g, Table 3, Entry 6)



According to the general procedure, the reaction of 1-(4-(methoxycarbonyl)benzoyl)pyrrolidine-2,5-dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 93% yield (44.7 mg). White solid. <u>¹H NMR (500 MHz, CDCl₃)</u> δ 8.18-8.16 (d, *J* = 8.1 Hz, 2 H), 7.87-7.86 (d, *J* = 8.1 Hz, 2 H), 7.83-7.82 (d, *J* = 8.2 Hz, 2 H), 7.66-7.63 (t, *J* = 7.5 Hz, 1 H), 7.54-7.51 (t, *J* = 7.7 Hz, 2 H), 3.99 (s, 3 H). <u>¹³C NMR (125 MHz, CDCl₃)</u> δ 196.07, 166.34, 141.34, 136.97, 133.24, 132.97, 130.12, 129.80, 129.52, 128.48, 52.49.

1-(Thiophene-2-carbonyl)pyrrolidine-2,5-dione (1h, Table 3, Entry 7)



According to the general procedure, the reaction of 1-(thiophene-2-carbonyl)pyrrolidine-2,5dione (0.20 mmol), phenylboronic acid (3.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (4.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 86% yield (32.4 mg). Colorless oil. ¹<u>H NMR (500 MHz,</u> <u>CDCl₃</u>) δ 7.90-7.89 (d, *J* = 8.2 Hz, 2 H), 7.76-7.75 (d, *J* = 4.9 Hz, 1 H), 7.68-7.67 (d, *J* = 3.7 Hz, 1 H), 7.64-7.61 (t, *J* = 7.5 Hz, 1 H), 7.54-7.51 (t, *J* = 7.7 Hz, 2 H), 7.20-7.19 (t, *J* = 4.8 Hz, 1 H). ¹³<u>C NMR (125 MHz, CDCl₃)</u> δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

1-(Cyclohexanecarbonyl)pyrrolidine-2,5-dione (1i, Table 3, Entry 8)



According to the general procedure, the reaction of 1-(cyclohexanecarbonyl)pyrrolidine-2,5dione (0.20 mmol), phenylboronic acid (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%) and Na₂CO₃ (2.5 equiv) in dioxane (0.25 M) for 15 h at 120 °C, afforded after work-up and chromatography the title compound in 86% yield (32.4 mg). Colorless oil. ¹H NMR (500 MHz, <u>CDCl₃</u>) δ 7.98-7.96 (d, *J* = 8.2 Hz, 2 H), 7.58-7.56 (t, *J* = 7.5 Hz, 1 H), 7.50-7.47 (t, *J* = 7.7 Hz, 2 H), 3.31-3.27 (t, *J* = 11.5 Hz, 1 H), 1.93-1.86 (m, 4 H), 1.78-1.75 (d, *J* = 11.7 Hz, 1 H), 1.54-1.49 (t, *J* = 13.4 Hz, 2 H), 1.46-1.39 (m, 2 H), 1.34-1.31 (d, *J* = 12.5 Hz, 1 H). ¹³C NMR (125 MHz, <u>CDCl₃</u>) δ 203.92, 136.38, 132.73, 128.59, 128.27, 45.65, 29.44, 25.98, 25.88.

Selectivity Studies – Boronic Acids

<u>*General Procedure.*</u> An oven-dried vial equipped with a stir bar was charged with an amide substrate (0.1 mmol, 1.0 equiv), two boronic acid substrates (each 2.0 equiv), $Pd(OAc)_2$ (0.03 equiv), PCy_3HBF_4 (0.12 equiv) and sodium carbonate (2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Table ESI-1. Selectivity Study in the Cross-Coupling of 1-Benzoylpyrrolidine-2,5-dione.^a



Entry	2-I	2-II	Boronic acid	3-I:3-II				
	(\mathbf{R}_1)	(R ₂)	(equiv)	$\left(\mathbf{R}_{1}:\mathbf{R}_{2}\right)^{b}$				
1	MeO-	CF ₃ -	2.0	1:2.77				

^{*a*}Conditions: Pd(OAc)₂ (3.0 mol%), PCy₃HBF₄ (12 mol%), dioxane (0.25 M), 120 °C, 15 h. All reactions carried out using standard Schlenk techniques under. ^{*b*}Determined by ¹H NMR and/or GC-MS.

Selectivity Studies – Amides

<u>*General Procedure.*</u> An oven-dried vial equipped with a stir bar was charged with two amide substrates (each 0.2 mmol, 1.0 equiv), phenylboronic acid (0.5 equiv), $Pd(OAc)_2$ (0.03 equiv), PCy_3HBF_4 (0.12 equiv) and sodium carbonate (2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Table ESI-2. Selectivity Study in the Cross-Coupling of 1-Benzoylpyrrolidine-2,5-dione.^a



Entry	1-I	1-II	Amide	3-I:3-II			
	(R_1)	(R ₂)	(equiv)	$\left(R_1:R_2\right)^b$			
1	MeO-	CF ₃ -	2.0	1:32.47			

^{*a*}Conditions: Pd(OAc)₂ (3.0 mol%), PCy₃HBF₄ (12 mol%), dioxane (0.25 M), 120 °C, 15 h. All reactions carried out using standard Schlenk techniques under. ^{*b*}Determined by ¹H NMR and/or GC-MS.

Selectivity Studies – Succinimide vs. Glutarimide

<u>*General Procedure.*</u> An oven-dried vial equipped with a stir bar was charged with two amide substrates (each 0.2 mmol, 1.0 equiv), phenylboronic acid (0.5 equiv), $Pd(OAc)_2$ (0.03 equiv), PCy_3HBF_4 (0.12 equiv) and sodium carbonate (2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Table ESI-3. Selectivity Study in the Cross-Coupling of 1-Benzoylpyrrolidine-2,5-dione.^a



Entry	1-I (amide)	1-II (amide)	Amide (equiv)	3-I:3-II $(R_1:R_2)^b$			
1	N-succinimide	<i>N</i> -glutarimide	2.0	1:3.48			

^{*a*}Conditions: Pd(OAc)₂ (3.0 mol%), PCy₃HBF₄ (12 mol%), dioxane (0.25 M), 120 °C, 15 h. All reactions carried out using standard Schlenk techniques under. ^{*b*}Determined by ¹H NMR and/or GC-MS.

References

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ESI-21







130 120 110 100 90 80 70 6	60 50 40 30 20	20 10 0 -10 -20 -3 f1 (ppm)	30 -40 -50 -60	-70 -80 -90	-100 -110 -120 -130



ESI-25



ESI-26



ESI-27



ESI-28



ESI-29



ESI-30





ESI-32



----63.00

10	0	-10	-20	-30	-40	-50	-60	-70	-80	-90	-100	-110	-120	-130	-140	-150	-160	-170	-180	-190	-200	-210
											f1 (ppm))										



110 100 90 f1 (ppm) 140 130 Ó -10

ESI-34



ESI-35



ESI-36



ESI-37







ESI-40



ESI-41



ESI-42

7.90 7.75 7.75 7.75 7.67 7.67 7.61 7.61 7.61 7.61 7.53 7.53 7.53 7.51 7.51 7.51 7.51 7.51 7.51 7.53 7.720 7.19 7.719



ESI-43



ESI-44