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Micellar Suzuki Cross-Coupling between Thiophene and Aniline in Water and under Air

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Abstract: The Suzuki–Miyaura cross-coupling reaction plays a fundamental role in modern synthetic organic chemistry, both in academia and industry. For this reason, scientists continue to search for new, more effective, cheaper and environmentally friendly procedures. Recently, micellar synthetic chemistry has been demonstrated to be an excellent strategy for achieving chemical transformations in a more efficient way, thanks to the creation of nanoreactors in aqueous environments using selected surfactants. In particular, the cheap and commercially available surfactant Kolliphor EL (a polyethoxylated castor oil derivative) has been used with success to achieve metal-catalyzed transformations in water with high yields and short reaction times, with the advantage of using air-sensitive catalysts without the need for inert atmosphere. In this work, the Kolliphor EL methodology was applied to the Suzuki cross-coupling reaction between thiophene and aniline, using the highly effective catalyst Pd(dtbpf)Cl_2. The cross-coupling products were achieved at up to 98% yield, with reaction times of up to only 15 min, working at room temperature and without the need for inert atmosphere.

Keywords: micellar synthesis; cross coupling; Suzuki reaction; thiophene; aniline

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1. Introduction

Since its discovery in 1979 [1], the Suzuki–Miyaura cross-coupling reaction has been used as an election tool for organic synthesis, both in discovery chemistry and manufacturing processes, due to its broad functional-group tolerance; its reproducibility; and its use of stable, environmentally benign, inexpensive and readily prepared boron reagents [2–6]. Despite the huge advances attained after its introduction, there is still room for improvement, in particular regarding the use of ecocompatible reaction media and shorter reaction times to minimize energy consumption in scaling processes. Recently, surfactant-mediated micellar catalysis has emerged in the field of organic chemistry, allowing synthetic transformation in water with excellent results in term of reaction kinetics, yields and ecocompatibility [7–10]. The key is the use of selected surfactants able to form association colloids (micelles) of organic molecules in water that behave similarly to nano- and microreactors, whereby organic transformations can occur efficiently due to the mutual proximity of the reagent and catalyst, somehow mimicking what nature has done within cells for billions of years. Thus, C-C and C-N bond-forming reactions, and several other organic transformations, have been successfully achieved with micellar procedures, with substantial improvements with respect to classic organic solvent methodologies [11–16]. Within these, the commercially available surfactant Kolliphor EL (a polyethoxylated castor oil, shown in Figure 1) has been proven to form oxygen free micelles, enabling cross-coupling reactions without the need for deoxygenation of the reaction environment [17,18].

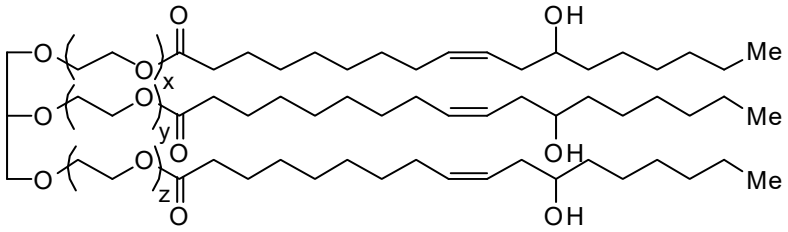


Figure 1. Chemical structure of Kolliphor EL.

Within this context, we were interested in the preparation of thiophene-substituted anilines to be used as precursors for the synthesis of complex heterocyclic systems [19–22]. Beyond this, thiophene-substituted anilines also serve to produce conductive polymers [23] and as ligand precursors for coordination chemistry [24–26]. The obvious strategy for their production involves the cross-coupling processes starting from selected aniline and thiophene precursors, with the Suzuki–Miyaura process being the reaction of choice. In this work, we explored the Kolliphor EL methodology for the Suzuki cross-coupling reaction between thiophenes and anilines, using the highly effective catalyst Pd(dtbpf)Cl_2 [27], in comparison to reported classic procedures. The reactions of 2-, 3- and 4-bromoaniline with 2- and 3-thienyl boronic acids and of 2- and 3-bromothiophene with 2-, 3- and 4-aniline boron reagents were tested, as well as 2,4-, 3,4-, 2,5- and 3,5-dibromoaniline with 2- and 3-thienyl boronic acids. Excellent results were obtained in terms of the isolated yields and reaction kinetics with respect to classical organic solvent procedures.

2. Materials and Methods

2.1. General Information

All reagents and solvents were purchased from commercial sources (Merck Life Science S.r.l., Milan, Italy, Fluorochem Ltd., Hadfield, United Kingdom, and TCI Europe N.V., Zwijndrecht, Belgium) and used without further purification. Ultra-Turrax T25 (IKA-Werke GmbH and Co. KG, Staufen, Germany) was used for the Kolliphor EL–toluene mixing. NMR spectra (copies in the Supplementary Materials) were recorded with a Bruker AVANCE III HD 400 MHz spectrometer (Bruker corp., Billerica, MA, USA) (^{1}H:400 MHz, ^{13}C:101 MHz). Chemical shifts (δ) are expressed in parts per million (ppm). Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded with a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory (PerkinElmer Inc., Waltham, MA, USA). Melting points were measured with a Stanford Research Systems Optimelt apparatus (SRS, Sunnyvale, CA, USA). Elemental analyses were obtained with an Elementar vario MICRO cube instrument (Elementar Analysensysteme GmbH, Langenselbold, Germany).

2.2. General Procedure 1: Micellar Suzuki Cross-Coupling between Monobromoanilines and Thiophene Boronic Acids

A mixture of bromoaniline **1a–c** (0.5 mmol), thiophene boronic acid **2a–b** (0.6 mmol), Pd(dtbpf)Cl_2 (0.01 mmol), Et_3N (1 mmol) and aqueous Kolliphor EL (2 mL, 1.97% H_2O) was stirred (500 rpm) at r.t. for the time stated in the text. EtOH was then added (approximately 10 mL, till the reaction mixture was homogeneous) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/*n*-hexane 8:2) to afford the desired product **3aa-cb** in pure form.

2-(2-Thienyl)aniline (**3aa**). Yellowish solid; mp 35 °C; R_f = 0.28; IR (ATR): 3445, 3363, 3101, 3069, 3021 1612, 1488, 1453, 1302, 1245, 1195, 1158, 1142, 1036, 957, 849, 818, 747, 695, 617, 543 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.27–7.14 (m, 3H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.03 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 141.2, 131.0, 129.1, 127.6, 125.9, 125.3, 120.0, 118.6, 115.9; The spectroscopic data are in accordance to those reported in the literature [25].

2-(3-Thienyl)aniline (**3ab**). Light brown solid; mp 40 °C; R_f = 0.26; IR (ATR) 3445, 3356, 3098, 3073, 3028, 1613, 1487, 1452, 1360, 1298, 1262, 1192, 1157, 1081, 1048, 1022, 937, 896, 861, 836, 786, 746, 701, 650, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.39 (dd, *J* = 2.8, 1.3 Hz, 1H), 7.29 (dd, *J* = 4.8, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.16 (td, *J* = 7.7, 1.5 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.78 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.85 (br, 2H). The spectroscopic data are in accordance to those reported in the literature [26].

3-(2-Thienyl)aniline (**3ba**). Yellowish oil; R_f = 0.27; IR (ATR): 3438, 3356, 3101, 3069, 3040, 1617, 1598, 1581, 1485, 1453, 1304, 1230, 1198, 1168, 1079, 1048, 993, 858, 827, 775, 688, 609, 558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.14 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.97–6.90 (m, 2H), 6.81 (t, *J* = 2.0 Hz, 1H), 6.48 (ddd, *J* = 7.9, 2.3, 0.9 Hz, 1H), 3.47 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 144.7, 135.4, 129.9, 127.9, 124.6, 123.1, 116.5, 114.4, 112.6; Anal. Calcd. for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.58; H, 5.16; N, 7.95.

3-(3-Thienyl)aniline (**3bb**). White solid; mp 85 °C; R_f = 0.26; IR (ATR): 3398, 3300, 3204, 3099, 2922, 2852, 1597, 1583, 1530, 1494, 1460, 1367, 1286, 1227, 1192, 1091, 993, 864, 843, 765, 681, 646, 560, 533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 2.4, 1.9 Hz, 1H), 7.28–7.24 (m, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.92 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 6.84–6.82 (m, 1H), 6.54 (ddd, *J* = 7.9, 2.3, 0.9 Hz, 1H), 3.58 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 142.5, 136.9, 129.7, 126.4, 126.0, 120.2, 117.1, 114.0, 113.2; Anal. Calcd. for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.55; H, 5.14; N, 8.01.

4-(2-Thienyl)aniline (**3ca**). Light brown solid; mp 76 °C; R_f = 0.28; IR (ATR): 3440, 3356, 3195, 3097, 2922, 2852, 1614, 1603, 1531, 1499, 1429, 1407, 1286, 1256, 1182, 1132, 1081, 1050, 954, 846, 809, 698, 660, 636, 571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 4.4 Hz, 1H), 7.04 (dd, *J* = 4.7, 3.9 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 1H). The spectroscopic data are in accordance to those reported in the literature [28].

4-(3-Thienyl)aniline (**3cb**). Yellow solid; mp 97 °C; R_f = 0.26; IR (ATR): 3401, 3306, 3207, 3096, 3039, 1625, 1603, 1537, 1504, 1439, 1365, 1268, 1256, 1204, 1189,1130, 1094, 855, 827, 775, 687, 671, 623, 567, 509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.38–7.33 (m, 2H), 7.31 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.75–6.70 (m, 2H), 3.70 (br, 2H). The spectroscopic data are in accordance to those reported in the literature [24].

2.3. General Procedure 2: Micellar Suzuki Cross-Coupling between Anilines Boronic Acids and Esters and Bromo-Thiophenes

A mixture of aniline boronic acid **4a–b** or ester **4c** (0.6 mmol), bromo-thiophene **5a–b** (0.5 mmol), Pd(dtbpf)Cl_2 (0.01 mmol), Et_3N (1 mmol) and Kolliphor EL (1.97%, H_2O)/toluene 9:1 (2 mL, premixed with Ultra-Turrax at 20,000 rpm for 5 min), was stirred (500 rpm) at 60 °C for the time stated in the text. EtOH was then added (approximately 10 mL, until the reaction mixture was homogeneous) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/*n*-hexane8:2) to afford the desired product **3aa–cb** in pure form.

2.4. General Procedure 3: Micellar Suzuki Cross-Coupling between Dibromoanilines and Thiophene Boronic Acids

A mixture of dibromoaniline **6a–d** (0.5 mmol), thiophene boronic acid **2a–b** (1.2 mmol), Pd(dtbpf)Cl_2 (0.01 mmol), Et_3N (2 mmol) and Kolliphor EL (1.97%, H_2O)/toluene 9:1 (2 mL, premixed with Ultra-Turrax at 20,000 rpm for 5 min) was stirred (500 rpm) at 60 °C for the time stated in the text. EtOH was then added (approximately 10 mL, until the reaction mixture was homogeneous) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/*n*-hexane 8:2) to afford the desired product **7aa–db** in pure form.

2,4-di-(2-Thienyl)aniline (**7aa**). Yellowish oil; R_f = 0.34; IR (ATR): 3459, 3370, 3208, 3101, 3068, 3021, 1615, 1534, 1491, 1429, 1405, 1343, 1295, 1260, 1233, 1212, 1183, 1157, 1078, 1048, 944, 888, 845, 811, 689, 616, 564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.39 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.24 (dd, *J* = 3.5, 1.1 Hz, 1H), 7.21–7.17 (m, 2H), 7.15 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.05 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.78 (d,

J = 8.3 Hz, 1H), 4.09 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 143.7, 140.5, 128.7, 127.9, 127.6, 126.9, 126.2, 125.6, 125.2, 123.4, 121.6, 120.2, 116.1; Anal. Calcd. For $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.26; H, 4.36; N, 5.51.

2,5-di-(2-Thienyl)aniline (**7ba**). Yellowish solid; mp 80 °C; R_f = 0.36; IR (ATR): 3463, 3370, 3094, 3064, 2923, 2852, 1614, 1599, 1484, 1427, 1413, 1353, 1318, 1291, 1260, 1231, 1193, 1128, 1079, 1041, 940, 870, 844, 834, 814, 713, 690, 572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.34–7.30 (m, 2H), 7.29 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.24 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.15 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.11–7.06 (m, 2H), 7.03 (d, *J* = 1.8 Hz, 1H), 4.10 (br, 2H); The spectroscopic data are in accordance to those reported in the literature [24].

3,4-di-(2-Thienyl)aniline (**7ca**). Light brown solid; mp 75 °C; R_f = 0.32; IR (ATR): 3464, 3369, 3189, 3094, 3064, 3030, 1610, 1598, 1483, 1449, 1427, 1413, 1353, 1318, 1292, 1260, 1232, 1198, 1079, 845, 834, 813, 714, 690, 571, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.3 Hz, 1H), 7.15 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.11 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.87–6.81 (m, 2H), 6.77 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.73 (d, *J* = 2.5 Hz, 1H), 6.70 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.59 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.68 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 143.2, 142.9, 134.7, 132.2, 126.9, 126.8, 126.8, 126.3, 125.7, 125.0, 124.0, 117.1, 114.5; Anal. Calcd. For $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.39; H, 4.30; N, 5.43.

3,5-di-(2-Thienyl)aniline (**7da**). Yellow solid; mp 140 °C; R_f = 0.35; IR (ATR): 3420, 3307, 3203, 3101, 3066, 2953, 2921, 2851, 1623, 1590, 1525, 1434, 1364, 1319, 1231, 1198, 1078, 1028, 988, 851, 819, 751, 701, 689, 612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 3.6, 1.1 Hz, 2H), 7.31–7.27 (m, 3H), 7.09 (dd, *J* = 5.1, 3.6 Hz, 2H), 6.86 (d, *J* = 1.5 Hz, 2H), 3.78 (br, 2H). The spectroscopic data are in accordance to those reported in the literature [29].

2,4-di-(3-Thienyl)aniline (**7ab**). Yellow solid; mp 85 °C; R_f = 0.32; IR (ATR): 3443, 3355, 3095, 2954, 2922, 2852, 1615, 1493, 1432, 1400, 1364, 1342, 1294, 1260, 1231, 1200, 1186, 1157, 1084, 928, 857, 840, 828, 777, 737, 686, 633, 573 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.1 Hz, 1H), 7.29 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.27–7.23 (m, 2H), 7.21–7.19 (m, 2H), 7.18–7.14 (m, 2H), 6.62 (d, *J* = 8.2 Hz, 1H), 3.66 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 142.3, 139.7, 139.7, 128.4, 128.3, 126.7, 126.3, 126.2, 126.0, 122.8, 122.7, 118.3, 116.1; Anal. Calcd. For $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.28; H, 4.34; N, 5.47.

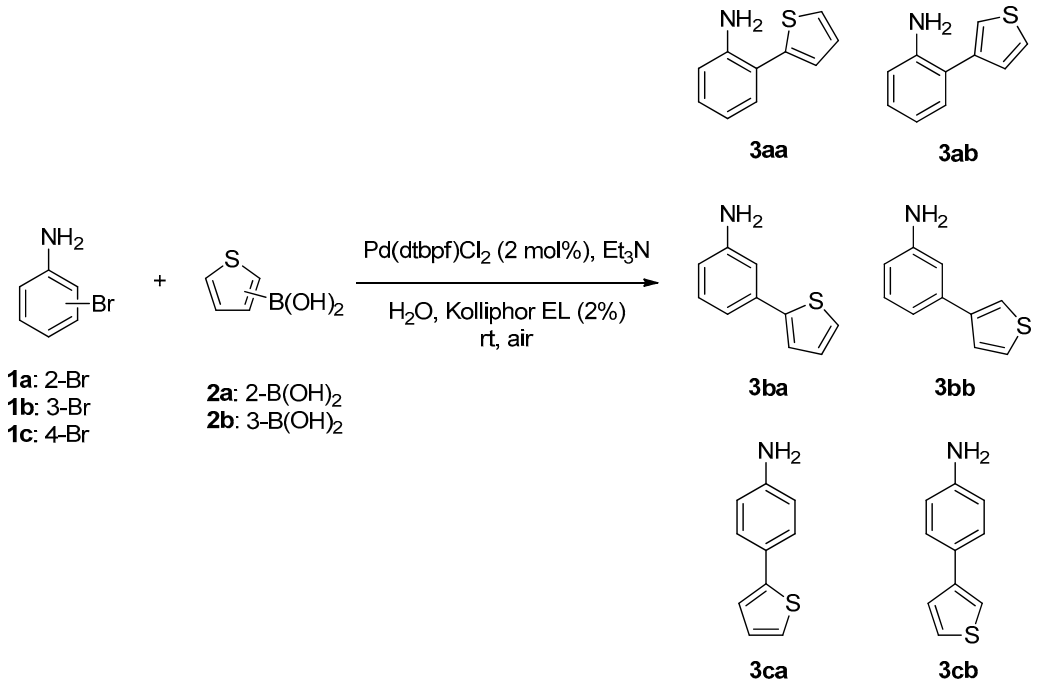
2,5-di-(3-Thienyl)aniline (**7bb**). Yellow solid; mp 124 °C; R_f = 0.33; IR (ATR): 3425, 3350, 3097, 2951, 2922, 2852, 1614, 1561, 1493, 1433, 1357, 1314, 1294, 1267, 1196, 1183, 1084, 947, 862, 846, 778, 738, 705, 649, 609, 583, 552, 520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.41 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.39–7.36 (m, 1H), 7.29 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.01 (d, *J* = 1.7 Hz, 1H), 3.92 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 142.2, 139.5, 136.1, 130.6, 128.3, 126.4, 126.1, 126.0, 122.5, 121.5, 120.2, 117.0, 113.6; Anal. Calcd. For $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.40; H, 4.31; N, 5.42.

3,4-di-(3-Thienyl)aniline (**7cb**). Brown solid; mp 79 °C; R_f = 0.29; IR (ATR): 3442, 3356, 3096, 2955, 2920, 2850, 1602, 1576, 1537, 1476, 1359, 1303, 1261, 1239, 1189, 1080, 1024, 940, 855, 845, 825, 779, 737, 693, 679, 662, 648, 612, 594, 566, 518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.2 Hz, 1H), 7.08–7.01 (m, 2H), 6.95 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.85 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.69 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 6.64 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.58 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.55 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 141.2, 141.1, 135.2, 130.2, 128.1, 127.9, 124.9, 123.5, 123.2, 121.6, 120.6, 115.5, 113.2; Anal. Calcd. For $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.44; H, 4.28; N, 5.39.

3,5-di-(3-Thienyl)aniline (**7db**). White solid; mp 155 °C; R_f = 0.32; IR (ATR): 3424, 3302, 3203, 3104, 3090, 2953, 2923, 2853, 1625, 1593, 1526, 1449, 1374, 1352, 1314, 1274, 1226, 1189, 1093, 992, 933, 875, 848, 834, 773, 684, 643, 619, 574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.32–7.27 (m, 4H), 7.14 (t, *J* = 1.5 Hz, 1H), 6.77 (d, *J* = 1.5 Hz, 2H), 3.66 (br, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 142.4, 137.5, 126.5, 126.1, 120.5, 115.7, 112.2; Anal. Calcd. for $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.28; H, 4.34; N, 5.47.

3. Results and Discussion

We started our investigation by reacting 2-bromoaniline **1a** with 2-thienylboronic acid **2a** (Scheme 1), taking a cue from the optimized conditions reported earlier [18]. Thus, **1a** (0.5 mmol), **2a** (0.6 mmol), Pd(dtbpf)Cl_2 (2% mol) and Et_3N (1 mmol) were added to 2 mL of a 2 w% Kolliphor EL solution in water and stirred at rt under air. Surprisingly, after only 15 min, TLC control showed no presence of starting materials. Proceeding with the reaction workup, **3aa** was isolated at 86% chemical yield (Table 1, Entry 1). Under these conditions, thienyl-anilines **3ab**, **3bb**, **3ca** and **3cb** (Scheme 1) were obtained at yields of 81%, 88%, 91% and 94%, respectively (Table 1, Entries 2, 4, 5 and 6, respectively). The reaction of 3-bromoaniuline **1b** with 2-thienyl boronic acid **2a** was less effective (Table 1, Entry 3); extending the reaction time from 15 to 60 min was enough to increase the yield from 64% to 96% (Table 1, Entry 7). For comparison, we reported in Table 1 (Entries 8–10) classical organic solvent procedures present in the literature carried out with the same class of Pd catalyst, i.e., L_2PdCl_2 [23,25,30]. The yields were comparable, even if in two cases they were slightly lower, although classic procedures require at least 12 h at higher temperature to complete the transformations and under inert atmosphere.



Scheme 1. Micellar Suzuki cross-coupling between mono-bromoanilines and thienyl boronic acids.

Stimulated by these results, we tested our methodology inverting the functionalities on starting materials, i.e., boron on aniline and bromine on thiophene (Scheme 2). Surprisingly, the reactions with previous conditions were much less effective (Table 2, Entries 1–4), as starting materials consuming needed 20 h and products were isolated in poor yields (22–45%). In the past, we overcame this unfavorable behavior by resorting to the cosolvent approach [19], i.e., the addition of a 10 v% of water immiscible organic solvent leading to the formation of a micro-emulsion, whereby the cores of the micelles swell, giving more space for the reactions to happen. Thus, we re-ran the reactions by adding a 10 v% of toluene to the Kolliphor EL water solution (vigorous premixing is essential for the micro-emulsion to form). This was beneficial for the kinetics (1 h vs. 20 h), but yields remained low to modest (Table 2, Entries 5–10). Temperature is another factor to consider in micellar procedures, as a slight increment could enormously increase reaction outputs [21]; obviously, the emulsion cloud point must not be exceeded, otherwise the micellar environment will be destroyed [31]. The temperature was increased to 60 °C and products **3aa–cb** were obtained in excellent yields, ranging from 88 to 96% (Table 2, Entries 11–16). To prove

the combined effect of cosolvent and temperature, we attempted the reaction of **4c** with **5b** at 60 °C without the addition of toluene, whereby the yield dropped from 96 to 75% (Table 2, Entry 17). Clear advantages of the use of Kolliphor EL methodology respect to reported classical ones in organic solvent and inert atmosphere could be seen also for these kinds of reactions (Table 2, Entries 18 and 19) [32,33].

Table 1. Output of micellar Suzuki cross-coupling between mono-bromoanilines and thienyl boronic acids.

Entry	Br-Aniline	Thienyl-B(OH)$_2$	Time	Temperature	Product	Yield% [1]
1	**1a**	**2a**	15 min	rt	**3aa**	86
2	**1a**	**2b**	15 min	rt	**3ab**	81
3	**1b**	**2a**	15 min	rt	**3ba**	64
4	**1b**	**2b**	15 min	rt	**3bb**	88
5	**1c**	**2a**	15 min	rt	**3ca**	91
6	**1c**	**2b**	15 min	rt	**3cb**	94
7	**1b**	**2a**	60 min	rt	**3ba**	96
8 [2]	**1a**	**2a**	12 h	70 °C	**3aa**	74
9 [3]	**1a**	**2b**	24 h	80 °C	**3ab**	94
10 [4]	**1c**	**2a**	16 h	80 °C	**3ca**	74

[1] Isolated yields. [2] Organic solvent procedure with L_2PdCl_2 catalyst in inert atmosphere reported in [25]. [3] Organic solvent procedure with L_2PdCl_2 catalyst in inert atmosphere reported in [30]. [4] Organic solvent procedure with L_2PdCl_2 catalyst in inert atmosphere reported in [23].

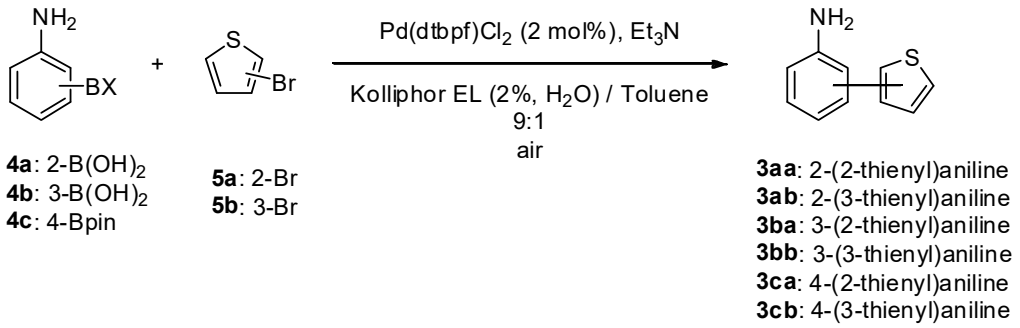
Table 2. Output of micellar Suzuki Cross-Coupling between aniline boronic acids and esters and bromo-thiophenes.

Entry	Aniline-B	Br-Thiophene	Time	Temperature	Product	Yield% [1]
1 [2]	**4a**	**5a**	20 h	rt	**3aa**	22
2 [2]	**4b**	**5a**	20 h	rt	**3ba**	34
3 [2]	**4c**	**5a**	20 h	rt	**3ca**	45
4 [2]	**4a**	**5b**	20 h	rt	**3ab**	34
5	**4a**	**5a**	1 h	rt	**3aa**	31
6	**4b**	**5a**	1 h	rt	**3ba**	40
7	**4c**	**5a**	1 h	rt	**3ca**	51
8	**4a**	**5b**	1 h	rt	**3ab**	70
9	**4b**	**5b**	1 h	rt	**3bb**	50
10	**4c**	**5b**	1 h	rt	**3cb**	54
11	**4a**	**5a**	1 h	60 °C	**3aa**	95
12	**4b**	**5a**	1 h	60 °C	**3ba**	90
13	**4c**	**5a**	1 h	60 °C	**3ca**	88
14	**4a**	**5b**	1 h	60 °C	**3ab**	95
15	**4b**	**5b**	1 h	60 °C	**3bb**	90
16	**4c**	**5b**	1 h	60 °C	**3cb**	96
17 [2]	**4c**	**5b**	1 h	60 °C	**3cb**	75
18 [3]	**4b**	**5a**	12 h	60 °C	**3ba**	23
19 [4]	**4b**	**5b**	16 h	90 °C	**3bb**	82

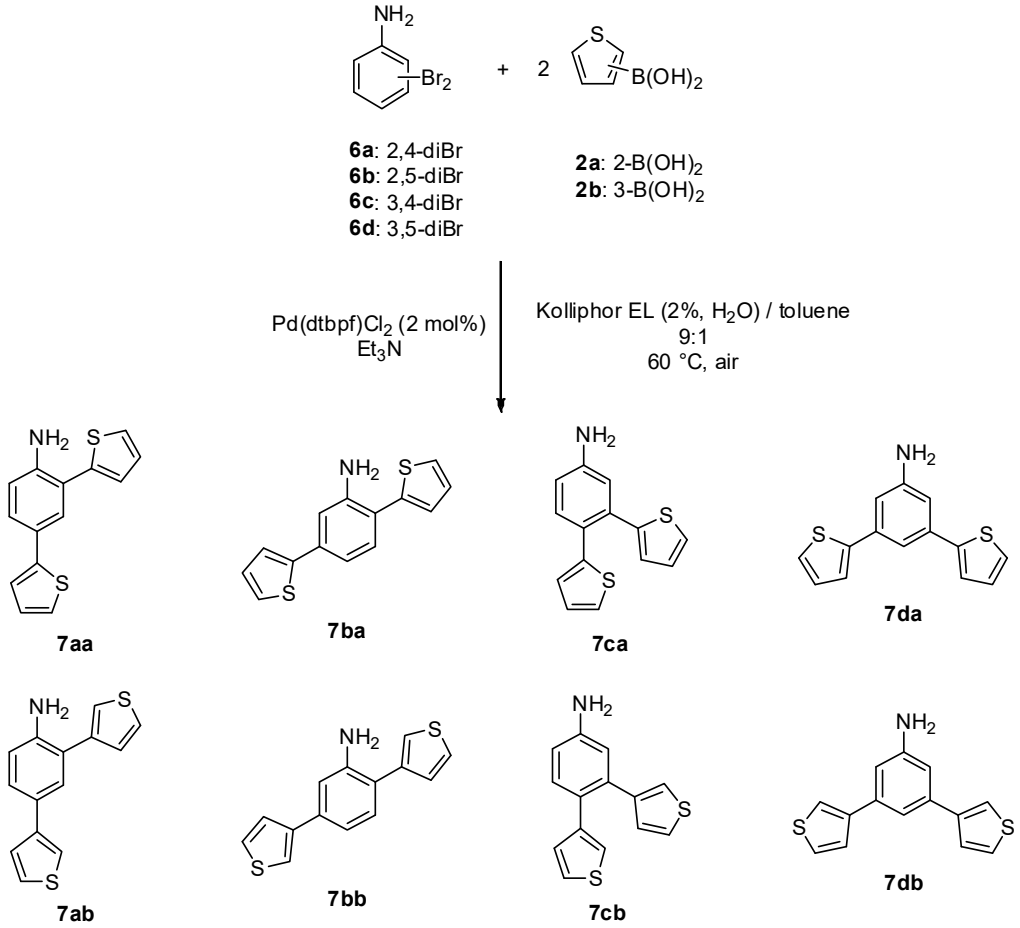
[1] Isolated yields. [2] Reaction carried without toluene as cosolvent. [3] Organic solvent procedure in inert atmosphere reported in [32]. [4] Organic solvent procedure in inert atmosphere reported in [33].

Finally, the Kolliphor-EL-mediated Suzuki reaction was tested for the thienyl functionalization of di-bromoanilines (Scheme 3). As observed for anilines boronic acids, the use of sole water–surfactant medium at rt resulted in slow kinetics and poor yields. Therefore, we opted for the use of 10 v% toluene as a cosolvent at 60 °C for 1 h (the results are presented in Table 3). These conditions allowed us to obtain di-thienyl-substituted anilines **7aa–db** in excellent isolated yields, ranging from 85% for 3,4-di-(3-thienyl)aniline **7cb** (Table 3, Entry 7) to 98% for 2,4-di-(2-thienyl)aniline **7aa** and 2,4-di-(3-thienyl)aniline **7ab** (Table 3, Entries 1 and 5). Importantly, (dtbpf)$PdCl_2$ was used at the same molar ratio of mono-bromoanilines, ending in a 1 mol% ratio with respect to the C-Br bonds present, without loss of efficiency. A comparison with classical procedures was more difficult in this

case, as only one procedure is reported in the literature for the sole thienyl functionalization of di-bromoanilines (Table 3, Entry 9) [24]; however, 72 h at 95 °C afforded only 55% yield, confirming once again the advantage of the Kolliphor EL mediated micellar procedure.



Scheme 2. Micellar Suzuki cross-coupling between aniline boronic acids and esters and bromo-thiophenes.



Scheme 3. Micellar Suzuki cross-coupling between di-bromoanilines and thienyl boronic acids.

Table 3. Output of micellar Suzuki cross-coupling between di-bromoanilines and thienyl boronic acids.

Entry	DiBr-Aniline	B-Thiophene	Time	Temperature	Product	Yield% [1]
1	**6a**	**2a**	1 h	60 °C	**7aa**	98
2	**6b**	**2a**	1 h	60 °C	**7ba**	96
3	**6c**	**2a**	1 h	60 °C	**7ca**	90
4	**6d**	**2a**	1 h	60 °C	**7da**	90
5	**6a**	**2b**	1 h	60 °C	**7ab**	98
6	**6b**	**2b**	1 h	60 °C	**7bb**	86
7	**6c**	**2b**	1 h	60 °C	**7cb**	85
8	**6d**	**2b**	1 h	60 °C	**7db**	89
9 [2]	**6b**	**2a**	72 h	95 °C	**7ba**	55

[1] Isolated yields. [2] Organic solvent procedure in inert atmosphere reported in [24].

4. Conclusions

In summary, we tested the Kolliphor-EL-mediated micellar Suzuki–Miyaura reaction for the production of thienyl-substituted anilines. Mono-thienylanilines were efficiently prepared using a 2 w% Kolliphor EL water solution at rt under air for 15 min starting from bromoanilines, while cosolvent addition, at a slightly higher temperature for 1 h of reaction time, was needed when starting from aniline boronic acid or esters. Under these latter conditions, di-thienylanilines from di-bromoanilines were obtained in the best yields reported to date. This work demonstrated that Suzuki cross-coupling to thienyl substituted anilines can be efficiently performed with the Kolliphor EL micellar system in a very simple and cost-effective way compared to previously reported methods, working at low temperature, with short reaction times and in air.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/org2040025/s1. Images of ^{1}H and ^{13}C NMR spectra for unknown compounds and images of ^{1}H NMR spectra for known compounds.

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