Supporting Information

The first cross-coupling reactions on tetrazines

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Experimental Procedures

General. Unless otherwise indicated, all starting materials were obtained from commercial suppliers (Aldrich, Fisher, Merck) and were used without further purification including, acetone, acetonitrile, triethylamine, n-hexane, PPh₃, CuI, Pd(OAc)₂, PdCl₂(PPh₃)₂, phenylacetylene, 2-methyl-3-butyn-2-ol, 1-hexyne, trimethylsilylacetylene, MgSO₄. N-methylpyrrolidinone, N,N-dimethylacetamide (DMA), TEA were purged with argon prior to use. All reactions were performed under an atmosphere of argon. 6-Morpholino-chlorotetrazine (**1a**),^{1,2} 6-pyrrolidino-chlorotetrazine (**1b**),^{1,2} 6-diethylamino-chlorotetrazine (**1c**),² 6-butylamino-chlorotetrazine (**1d**),² 6-amino-chlorotetrazine (**1e**),³ 6-methoxy-chlorotetrazine (**1g**),² and 3,6-dichlorotetrazine (**1h**)¹ were prepared following published procedures. Analytical thin-layer chromatography (TLC) was performed on Polygram SIL G/UV 254 Pre-coated plastic TLC plates with 0.25 mm silica gel from Macherey-Nagel + Co. Silica gel column chromatography was carried out with Flash silica gel (0.040 – 0.063 mm) from Merck. Melting points were determined using a Büchi melting point apparatus. The ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-250 spectrometer in CDCl₃. Chemical shifts (δ) are expressed in parts per million using residual solvent protons as internal standards: chloroform (δ 7.26 for ¹H, δ 77.00 for ¹³C). Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet), dd (doublet doublet). Low resolution mass spectrometry was obtained on a VG 12-250 Mass Spectrometer (Ion source: EI+, 70eV, 250°C; interface: 250°C).

3-Chloro-6-(3',5'-dimethylpyrazol-1'-yl)-1,2,4,5-tetrazine (1f**):** 211 mg (0.92 mmol) potassium 6-(3',5'-dimethylpyrazol-1'-yl)-1,2,4,5-tetrazine-3-olate² was heated in 1.2 ml POCl₃ at 80°C for 4 hours. After removal of the volatiles in vacuum the crude product was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate to give 52 mg (27 %) of **1f** as red crystals. mp.: 79-80°C. ¹H NMR (CDCl₃; 250MHz): δ 6.22 (s, 1H), 2.71 (s, 3H), 2.39 (s, 3H); ¹³C NMR (CDCl₃, 62.5 MHz): δ 166.1, 158.4, 154.5, 145.8, 112.6, 14.7, 13.0. ; MS (EI, 70eV) *m/z* for C₇H₇N₆Cl (% relative intensity, ion): 212(7), 210(43), 121(100), 106(62), 96(6), 80(43), 67(37), 53(92). IR(KBr) *v*_{max} : 3106, 2929, 1722, 1583, 1493, 1460, 1395, 1201, 1114, 1078, 1058, 967 cm⁻¹. Anal. calcd. for C₇H₇N₆Cl: C, 39.92%; H, 3.35 %; N, 39.90 %; Found C, 40.40 %; H, 3.53 %; N, 37.15 %.

General procedure for the preparation of ethynyl tetrazines in Sonogashira coupling: A dry Schlenk-flask was charged with 38 mg PdCl₂(PPh₃)₂ (0.0535 mmol, 5 mol%), 10.4 mg CuI (0.0535 mmol, 5 mol%), and 1mL solvent. After the addition of 1.07 mmol 6-amino-3-chlorotetrazine, 300 μ L (218 mg, 2.14 mmol) triethylamine and 2.14 mmol acetylene derivative the reaction mixture was purged with argon, sealed and stirred in an 80 °C oil bath until completion (by TLC). After evaporation of the solvent the remaining residue was purified by column chromatography using silica gel and hexane-aceton eluent mixtures.

General procedure for the preparation of ethynyl tetrazines in Negishi coupling: A dry Schlenk-flask was charged with 40.4 mg Pd(PPh₃)₄ (0.035 mmol, 7%), 0.5 mmol 3-amino-6-chloro-1,2,4,5-tetrazine. Than 1 mmol of 1-hexynylzinc chloride in 2mL THF, prepared according to the literature,⁴ was added dropwise, and the mixture was stirred at 60°C under argon until completion of the reaction. The solvent was evaporated, and the remaining residue was purified by column chromatography on silica gel with hexane-aceton eluent mixtures.

3a: The crude product was purified by silica gel column chromatography to afford 130 mg (0.52 mmol) of **3a** as a red solid. Yield: 52 %. mp.: 146-148°C; ¹H NMR (CDCl₃; 250MHz): δ 1.67 (s, 6H), 2.68 (s, 1H), 3.83-3.86 (m, 4H); ¹³C NMR (CDCl₃, 62.5 MHz): δ 30.9, 43.6, 65.4, 66.3, 76.1, 98.6, 150.1, 157.9; MS (EI, 70eV) m/z for C₁₁H₁₆N₅O₂ (% relative intensity, ion): 249(1), 234(1), 219(2), 151(68), 133(58), 123(52), 105(73), 93(56), 77(48), 69(57), 43(100). IR(KBr) ν_{max} : 3378, 2979, 2925, 2867, 1544, 1449, 1335, 1260, 1207, 1172, 1114, 1051, 969, 945 cm⁻¹; HRMS m/z calcd for C₁₁H₁₆N₅O₂ 250.1303[M+H]⁺, found 250.1307.

3b: The crude product was purified by silica gel column chromatography to afford 62 mg (0.23 mmol) of **3b** as a red solid. Yield: 23%. mp.: 184-186°C; ¹H NMR (CDCl₃; 250MHz): δ 3.84-3.88 (m, 4H), 4.03-4.07 (m, 4H), 7.39-7.43 (m, 3H), 7.63-7.68 (m, 3H); ¹³C NMR

(CDCl₃, 62.5 MHz): δ 43.6, 66.4, 83.0, 121.2, 128.5, 129.7, 132.2, 151.1, 157.7; MS (EI, 70eV) m/z for C₁₄H₁₄N₅O (% relative intensity, ion): 267(3), 202(17), 127(27), 112(57), 105(24), 42(100). IR(KBr) $\nu_{\max}$: 2957, 2912, 2861, 2215, 1535, 1448, 1344, 1261, 1116, 1044, 947, 847, 766 cm⁻¹; HRMS m/z calcd for C₁₄H₁₄N₅O 268.1198 [M+H]⁺, found 268.1187.

3c: The crude product was purified by silica gel column chromatography to afford 138 mg (0.56 mmol) of **3c** as a red solid. Yield: 56 %. mp.: 93-94°C; ¹H NMR (CDCl₃; 250MHz): δ 0.95 (t, 3H, J = 7.1Hz), 1.45-1.57 (m, 2H), 1.60-1.72 (m, 2H), 2.53 (t, 2H, J = 6.9Hz), 3.82-3.85 (m, 4H), 3.99-4.03 (m, 4H); ¹³C NMR (CDCl₃, 62.5 MHz): δ 13.5, 19.2, 30.0, 66.4, 74.8, 96.5, 151.0, 158.1; MS (EI, 70eV) m/z for C₁₂H₁₈N₅O (% relative intensity, ion): 248(2), 112(100), 82(23), 55(85), 42(72). IR(KBr) $\nu_{\max}$: 2958, 2916, 2862, 2236, 1539, 1444, 1340, 1314, 1245, 1113, 1055, 950, 845, 792 cm⁻¹; HRMS m/z calcd for C₁₂H₁₈N₅O 248.1511 [M+H]⁺, found 248.1507.

4a: The crude product was purified by silica gel column chromatography to afford 133 mg (0.57 mmol) of **4a** as a red solid. Yield: 57%. mp.: 143-145°C; ¹H NMR (CDCl₃; 250MHz): δ 1.66, (s, 3H), 2.06-2.12 (m, 4H), 2.58 (br, 1H), 3.72-3.78(m, 4H); ¹³C NMR (CDCl₃, 62.5 MHz): δ 25.2, 30.9, 46.7, 65.4, 76.4, 98.1, 149.7, 156.2; MS (EI, 70eV) m/z for C₁₁H₁₆N₅O (% relative intensity, ion): 233(1), 165(6), 151(100), 133(55), 105(62). IR(KBr) $\nu_{\max}$: 3346, 2979, 2932, 2880, 1566, 1461, 1363, 1325, 1210, 1172, 1057, 964 cm⁻¹; HRMS m/z calcd for C₁₁H₁₆N₅O 234.1354 [M+H]⁺, found 234.1353.

4b: The crude product was purified by silica gel column chromatography to afford 141 mg (0.56 mmol) of **4b** as a red solid. Yield: 56%. mp.: 90-91°C; ^1H NMR (CDCl_3 ; 250MHz): δ 1.99-2.04 (m, 4H), 3.67-3.72(m, 4H), 7.28-7.31 (m, 3H), 7.55-7.59(m, 2H); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ 25.1, 83.5, 93.3, 121.4, 128.4, 129.4, 132.0, 150.4, 156.0; MS (EI, 70eV) m/z for $\text{C}_{14}\text{H}_{14}\text{N}_5$ (% relative intensity, ion): 251(7), 183(19), 127(92), 96(98), 84(40), 42(100). IR(KBr) ν_{max} : 3052, 2964, 2875, 1562, 1483, 1332, 1044, 966, 757, 688 cm^{-1} ; HRMS m/z calcd for $\text{C}_{14}\text{H}_{14}\text{N}_5$ 252.1249 $[\text{M}+\text{H}]^+$, found 252.1246.

4c: The crude product was purified by silica gel column chromatography to afford 67 mg (0.29 mmol) of **4c** as a red solid. Yield: 29 %. mp.: 22-25°C; ^1H NMR (CDCl_3 ; 250MHz): δ 0.94 (t, 3H, $J = 7.1\text{Hz}$), 1.45-1.54 (m, 2H), 1.60-1.69 (m, 2H), 2.06-2.12 (m, 4H), 2.52 (t, 2H, $J = 6.9\text{Hz}$), 3.72-3.77 (m, 4H); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ 13.5, 19.2, 22.0, 25.2, 30.1, 46.6, 75.1, 95.7, 150.4, 156.5; MS (EI, 70eV) m/z for $\text{C}_{12}\text{H}_{18}\text{N}_5$ (% relative intensity, ion): 231(7), 188(5), 174(6), 160(6), 149(5), 96(76), 42(100). IR(KBr) ν_{max} : 2956, 2874, 1556, 1460, 1329, 1042, 954, 851 cm^{-1} ; HRMS m/z calcd for $\text{C}_{12}\text{H}_{18}\text{N}_5$ 232.1562 $[\text{M}+\text{H}]^+$, found 232.1573.

5a: The crude product was purified by silica gel column chromatography to afford 71 mg (0.3 mmol) of **5a** as a red solid. Yield: 30 %. mp.: 59-60°C; ^1H NMR (CDCl_3 ; 250MHz): δ 1.22 (t, 6H, $J = 7.1\text{ Hz}$), 1.63 (s, 6H), 3.52 (br, 1H), 3.74 (q, 4H, $J = 7.1\text{ Hz}$); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ 12.4, 30.8, 42.2, 65.2, 76.1, 98.3, 149.5, 157.0; MS (EI, 70eV) m/z for $\text{C}_{11}\text{H}_{18}\text{N}_5\text{O}$ (% relative intensity, ion): 235(13), 177(6), 98(40), 69(39), 55(100). IR(KBr) ν_{max} : 3437, 2979, 2938, 1550, 1440, 1344, 1206, 1172, 1125, 1089, 1050, 1016, 965 cm^{-1} ; HRMS m/z calcd for $\text{C}_{11}\text{H}_{18}\text{N}_5\text{O}$ 236.1511 $[\text{M}+\text{H}]^+$, found 236.1509.

5b: The crude product was purified by silica gel column chromatography to afford 121 mg (0.48 mmol) of **5b** as a red solid. Yield: 48%. mp.: 96-98°C; ^1H NMR (CDCl_3 ; 250MHz): δ 1.30 (t, 6H, $J = 7.1$ Hz), 3.84 (q, 4H, $J = 7.1$ Hz), 7.38- 7.41(m, 3H), 7.63-7.67(m, 2H); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ 12.5, 42.3, 83.4, 93.4, 121.5, 128.4, 129.5, 132.1, 150.4, 157.0; MS (EI, 70eV) m/z for $\text{C}_{14}\text{H}_{16}\text{N}_5$ (% relative intensity, ion): 253(12), 127(79), 98(90), 83(92), 55(100). IR(KBr) ν_{max} : 2971, 2935, 2229, 1552, 1495, 1441, 1358, 1090, 1043, 1019, 959, 764 cm^{-1} ; HRMS m/z calcd for $\text{C}_{14}\text{H}_{16}\text{N}_5$ 254.1405 $[\text{M}+\text{H}]^+$, found 254.1399.

5c: The crude product was purified by silica gel column chromatography to afford 154 mg (0.65 mmol) of **5c** as a red oil. Yield: 65%; ^1H NMR (CDCl_3 ; 250MHz): δ) 0.91 (t, 3H, $J = 7.1\text{Hz}$), 1.23 (t, 6H, $J = 7.1$ Hz), 1.42-1.52 (m, 2H), 1.56-1.65 (m, 2H), 2.48 (t, 2H, $J = 6.9\text{Hz}$), 3.77 (q, 4H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ 12.4, 13.4, 19.1, 21.9, 30.0, 42.1, 75.0, 95.6, 150.2, 157.2; MS (EI, 70eV) m/z for $\text{C}_{12}\text{H}_{20}\text{N}_5$ (% relative intensity, ion): 234(2), 176(2), 148(3), 108(5), 98(73), 83(100), 55(91). IR(KBr) ν_{max} : 2960, 2934, 2872, 2237, 1552, 1461, 1443, 1379, 1348, 1048, 1021, 953 cm^{-1} ; HRMS m/z calcd for $\text{C}_{12}\text{H}_{20}\text{N}_5$ 234.1718 $[\text{M}+\text{H}]^+$, found 234.1723.

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