Synthesis of Aryl Ketones or Ketimines by Pd-Catalyzed Arene C-H Addition to Nitriles

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Table of Contents	S1
General Procedures	S2-S4
Characterization data	S4-S9
References	S9
¹H and ¹³C NMR spectra	S10-S31

General

The ^1H and ^{13}C NMR spectra were recorded at 300 MHz or 400 MHz and 75 MHz or 100 MHz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). Low resolution mass spectra were recorded on a triple quadrupole mass spectrometer. High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. All melting points are uncorrected. All reagents were used as obtained commercially. The product characterization data, ^1H and ^{13}C NMR spectra for compounds **7**, **12**, **15**, **16**, **25**, **31** can be found in the “Supporting Information” from our previous communication.¹ The compounds **30**, **32**, **34**, **37** have been characterized before and the characterization data can be found in the literature.^{2,3,4}

The intermolecular reaction of nitriles and arenes (Table 2, entries 1-24; Table 3, step 1 in entries 1-6)

The arene (2.0 mmol), the nitrile (1.0 mmol), $\text{Pd}(\text{OAc})_2$ (0.10 mmol), DMSO (0.10 mL) and TFA (2.5 mL) were placed in a 6 dram vial. The vial was sealed and the contents were stirred and heated at the indicated temperature for 24 h. The ketone products were obtained using the following acid work-up procedure and the ketimine products were obtained by using the following basic work-up procedure.

Acidic work-up. Water (15 mL) was added to the vial and the resulting mixture was heated at 70 °C for 2 h. The mixture was then cooled and extracted with diethyl ether three times. The combined organic layers were dried over anhydrous MgSO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column.

Basic Work-up. The reaction mixture was cooled to room temperature, and then K_2CO_3 was added to the vial until no CO_2 bubbles were generated (*Caution: a large amount of CO_2 is generated due to the reaction of TFA and K_2CO_3*). The resulting mixture was extracted with diethyl ether three times. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column.

The intramolecular reaction of arylalkanenitriles (Table 2, entries 25-32)

The nitrile (0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), DMSO (0.2 mL) and TFA (5.0 mL) were placed in a 6 dram vial. The vial was sealed and the contents were stirred and heated at the indicated temperature for 24 h. The resulted mixture was then worked up according to the above acidic work-up procedure.

General procedure for the intramolecular cyclization leading to xanthenes (step 2 in eq. 3)

The (2-fluorophenyl)(2-hydroxyphenyl)methanone (0.25 mmol), K_2CO_3 (0.50 mmol) and acetone (15 mL) were placed in a round-bottom flask. The flask was sealed and the contents were stirred at 50 °C for 2 h. The suspension was then filtered through a pad of celite and washed with 50 mL of ethyl ether. The filtrate was concentrated to afford the desired xanthenes.

The intermolecular reaction of nitriles and boronic acids (Table 4, entries 1-7)

The nitrile (5.0 mmol), the boronic acid (1.0 mmol), $Pd(OAc)_2$ (0.10 mmol), DMSO (0.10 mL) and TFA (2.5 mL) were placed in a 6 dram vial. The vial was sealed and the

contents were stirred and heated at 90 °C for 24 h. The resulted mixture was then worked up according to the above acidic or basic work-up procedure.

Characterization data:

5-Bromo-2-hydroxybenzophenone (9).⁵ Light yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 6.98 (d, *J* = 9.2 Hz, 1H), 7.50-7.72 (m, 7H), 11.92 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 110.51, 120.60, 120.73, 128.84, 129.39, 132.66, 135.63, 137.39, 139.19, 162.35, 200.75; IR (CDCl₃, cm⁻¹) 3490 (br), 3023, 1646, 1590; MS (EI) *m/z* (rel intensity) 278 (100), 276 (M⁺, 98), 197 (36); HRMS (EI) calcd for C₁₃H₉BrO₂ 275.9776, found: 275.9780.

3-Bromo-2,4,6-trimethylphenyl-4'-bromophenylmethanimine (13). Yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 2.02 (s, 3H), 2.19 (s, 3H), 2.42 (s, 3H), 7.00 (s, 1H), 7.48-7.59 (m, 4H), 8.8-10.2 (br, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 19.62, 21.51, 24.29, 125.96, 126.35, 129.52, 130.35, 132.15, 133.14, 134.50, 136.35, 138.71, 139.03, 177.08; IR (CDCl₃, cm⁻¹) 3260, 3016, 2926, 1610, 1596; MS (EI) *m/z* (rel intensity) 383 (15),

381 (M^+ , 15), 301 (10), 221 (9), 44 (100); HRMS (EI) calcd for $C_{16}H_{15}Br_2N$ 380.9551, found: 380.9557.

14

2,3,5,6-Tetramethylphenyl-phenylmethanimine (14). Colorless oil: 1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 6H), 2.26 (s, 6H), 7.03 (s, 1H), 7.36-7.43 (m, 3H), 7.72-7.76 (m, 2H), 9.0-10.0 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.74, 20.04, 127.99, 128.76, 130.30, 131.16, 131.45, 134.40, 138.18, 141.17, 179.80; IR ($CDCl_3$, cm^{-1}) 3250, 3025, 2920, 2858, 1616, 1593; MS (EI) m/z (rel intensity) 237 (M^+ , 22), 222 (16), 40 (100); HRMS (EI) calcd for $C_{16}H_{16}ClN$ 237.1518, found: 237.1521.

17

4'-Chlorophenyl-2,4,6-trimethylphenylmethanimine (17). Light yellow oil: 1H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 2.33 (s, 3H), 6.92 (s, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.66 (d, $J = 8.8$ Hz, 2H), 8.8-10.2 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.83, 21.36, 128.66, 128.68, 129.04, 129.29, 134.41, 136.45, 137.42, 138.24, 177.65; IR ($CDCl_3$, cm^{-1}) 3250, 3023, 2920, 2858, 1618, 1599; MS (EI) m/z (rel intensity) 257 (M^+ , 80), 256 (100), 242 (20), 222 (18); HRMS (EI) calcd for $C_{16}H_{16}ClN$ 257.0971, found: 257.0975.

19

2'-Fluorophenyl-2,4,6-trimethylphenylmethanimine (19). Colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 2.14 (s, 6H), 2.31 (s, 3H), 6.89 (s, 2H), 7.06-7.15 (m, 2H), 7.36-7.50 (m, 2H), 8.8-10.2 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.20, 21.36, 116.86, 117.08, 124.52, 124.56, 128.68, 130.89, 130.91, 132.39, 132.48, 134.44, 138.09, 160.20, 162.73, 176.80; IR (CDCl_3 , cm^{-1}) 3245, 3032, 2963, 2868, 1642, 1605; MS (EI) m/z (rel intensity) 241 (M^+ , 80), 240 (100), 225 (22), 221 (28); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}\text{NF}$ 241.1267, found: 241.1269.

20

2'-Fluorophenyl-2,4,6-trimethoxyphenylmethanimine (20). White solid: mp 126-128 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 3.61 (s, 6H), 3.77 (s, 3H), 6.10 (s, 2H), 6.90-7.10 (m, 2H), 7.20-7.30 (m, 1H), 7.47-7.55 (m, 1H), 9.0-9.8 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.55, 56.01, 90.94, 112.37, 115.97, 116.27, 123.96, 124.01, 128.61, 130.43, 130.47, 131.15, 131.27, 158.52, 158.53, 159.27, 162.13, 162.61, 169.43; IR (CDCl_3 , cm^{-1}) 3255, 3032, 2963, 1642, 1608; MS (EI) m/z (rel intensity) 289 (M^+ , 30), 257 (40), 123 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}\text{FNO}_3$ 289.1114, found: 289.1118.

2'-Fluorophenyl-2,5-dimethoxyphenylmethanimine (21). Colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 3.58 (s, 3H), 3.78 (s, 3H), 6.85-7.20 (m, 5H), 7.40-7.55 (m, 1H), 7.65-7.68 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.05, 56.47, 113.41, 114.70, 115.91, 116.21, 119.58, 124.21, 124.26, 128.70, 129.91, 130.98, 131.01, 133.66, 133.77, 153.03, 153.05, 153.73, 159.51, 162.89, 192.53; IR (CDCl_3 , cm^{-1}) 3032, 2963, 2868, 1632, 1600; MS (EI) m/z (rel intensity) 260 (M^+ , 100), 245 (18); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{13}\text{FO}_3$ 260.0849, found: 260.0853.

2'-Fluorophenyl-(2-hydroxyl-5-methylphenyl)methanone (32a). Colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 2.23 (s, 3H), 6.96 (d, $J = 8.7$ Hz, 1H), 7.10-7.40 (m, 4H), 7.43-7.56 (m, 2H), 13.0 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.64, 116.40, 116.68, 118.30, 119.65, 124.54, 124.58, 128.47, 130.03, 130.07, 132.92, 133.03, 133.07, 133.10, 138.45, 160.97, 161.27, 198.73; IR (CDCl_3 , cm^{-1}) 3450 (br), 3032, 2960, 1642, 1600; MS (EI) m/z (rel intensity) 230 (M^+ , 100), 215 (21); HRMS (EI) calcd for $\text{C}_{14}\text{H}_{11}\text{FO}_2$ 230.0743, found: 230.0750.

33a

2'-Fluorophenyl-(2-hydroxyl-5-isopropylphenyl)methanone (33a). Colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 1.15 (d, $J = 6.9$ Hz, 6H), 2.79 (m, 1H), 6.99 (d, $J = 8.7$ Hz, 1H), 7.20-7.60 (m, 6H), 11.84 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.11, 33.36, 116.38, 116.66, 118.35, 119.57, 124.54, 124.59, 126.80, 130.19, 130.23, 130.77, 130.80, 133.04, 133.15, 135.81, 139.60, 157.71, 161.04, 161.50, 198.67; IR (CDCl_3 , cm^{-1}) 3500 (br), 2968, 2866, 1642, 1599; MS (EI) m/z (rel intensity) 258 (M^+ , 100), 243 (16); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{15}\text{FO}_2$ 258.1056, found: 258.1061.

33

2-Isopropylxanthone (33). Colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 1.32 (d, $J = 6.9$ Hz, 6H), 3.05 (m, 1H), 7.33-7.50 (m, 3H), 7.58-7.72 (m, 2H), 8.17 (d, $J = 2.4$ Hz, 1H), 8.35 (dd, $J = 1.8, 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.21, 33.91, 118.07, 118.16, 121.75, 122.03, 123.67, 123.93, 126.97, 134.01, 134.85, 144.92, 154.82, 156.41, 177.65; IR (CDCl_3 , cm^{-1}) 3027, 2950, 2870, 1648, 1605; MS (EI) m/z (rel intensity) 238 (M^+ , 100), 223 (16); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2$ 238.0994, found: 238.0999.

2-Chloroxanthone (35).⁶ White solid: mp 169-171 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.50 (m, 3H), 7.63-7.76 (m, 2H), 8.25-8.32 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 118.26, 119.98, 121.65, 122.87, 124.50, 126.23, 127.00, 129.91, 135.14, 135.41, 154.67, 156.23, 176.35; IR (CDCl₃, cm⁻¹) 3023, 1652, 1600; MS (EI) m/z (rel intensity) 230 (M⁺, 70), 135 (100); HRMS (EI) calcd for C₁₃H₇ClO₂ 230.0135, found: 230.0136.

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