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Palladium-catalyzed amination of 3-bromo-4-fluoro-acetophenone

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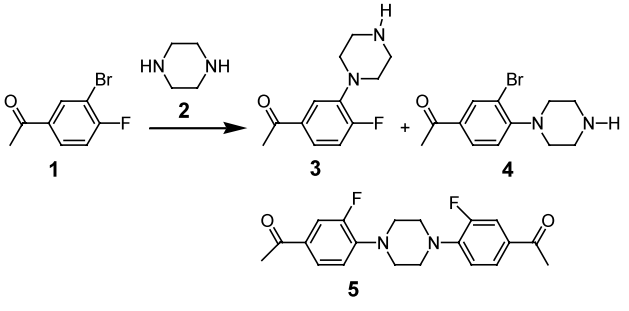
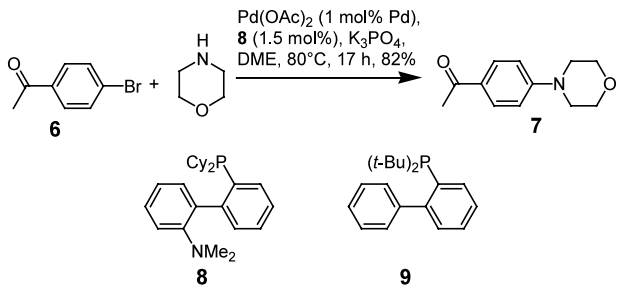
Abstract—The palladium-catalyzed amination of 3-bromo-4-fluoro-acetophenone was found to predominate over both the 4-fluoro nucleophilic substitution with amines and the palladium-catalyzed α-arylation of the acetyl group.

During the course of a medicinal chemistry program, we wanted to convert 3-bromo-4-fluoro-acetophenone (**1**) to arylpiperazine **3** through palladium-catalyzed amination with piperazine (**2**) (Scheme 1).[1] Reaction of aryl halides with piperazine under palladium-catalyzed conditions has been used to prepare *N*-arylpiperazines,[2] however, bis-arylation has been shown to be a potential problem.[2a,b] It is worth noting that compound **1** is an unique substrate for this type of amination reactions as it bears a fluorine *para* to an electron-withdrawing and yet enolizable ketone functionality. Palladium catalyzed α-arylation of ketones with aryl halides in the presence of a base has been well documented.[3] It is also well known that fluorobenzenes containing an *ortho*- or *para*-substituted electron-withdrawing groups undergo facile nucleophilic substitution with amines.[4] As the palladium-catalyzed amination reactions are usually carried out under basic conditions (Na*t*OBu, Cs_2CO_3, or K_3PO_4) at 80–100°C, we were concerned about the 4-fluoro nucleophilic substitution with amines. To our knowledge, the palladium-catalyzed amination on substrates with a fluorine *ortho* or *para* to an electron-withdrawing group has not yet been reported. This report describes our preliminary studies on acetophenone **1**.



Scheme 1.

Buchwald et al. had previously reported that the palladium-catalyzed amination of 4-bromoacetophenone (**6**) with morpholine (1.2 equiv.) in the presence of $Pd(OAc)_2$ (1 mol% Pd), ligand **8** (1.5 mol%), K_3PO_4 in DME at 80°C provided *N*-aryl morpholine **7** in good yield (Scheme 2).[1c,5] However, when we tried these conditions (Table 1, entry 1) in our case, we obtained a 1:9 mixture of the fluoride **3**[6] and bromide **4** (Scheme 1). After some experimentation, we found that reaction of **1** with piperazine (4 equiv.) gave a 9:1 mixture of **3** and **4** using $Pd(OAc)_2$ (10 mol% Pd), ligand **9** (10 mol%) in the presence of Cs_2CO_3 (1.5 equiv.) in benzene or toluene under reflux (method A) (Table 1, entries 2 and 3). Fluoride **3** was obtained in 80% yield after purification of the crude product through flash chromatography on silica gel. As shown in Table 1, the ratio of **3**:**4** appears to be dependent on the choice of the ligand (entry 4), Pd catalyst (entry 5), solvent (entry 6), and base (entry 7). In addition, the ratio of **3**:**4** was



Scheme 2.

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Table 1. Amination of 3-bromo-4-fluoro-acetophenone (**1**) with piperazine (**2**)

Entry	Conditions	**3**:**4**:**5**[a]
1	**2** (1.1 equiv.), $Pd(OAc)_2$ (1%), **8** (1.5%), K_3PO_4 (1.1 equiv.), DME, 80°C, 16 h	1:9:0
2	**2** (4 equiv.), $Pd(OAc)_2$ (10%), **9** (10%), Cs_2CO_3 (1.5 equiv.), C_6H_6, 80°C, 24 h (method A)	9:1:0
3	**2** (4 equiv.), $Pd(OAc)_2$ (10%), **9** (10%), Cs_2CO_3 (1.5 equiv.), $C_6H_5CH_3$, 110°C, 16 h (method A)	9:1:0
4	**2** (4 equiv.), $Pd(OAc)_2$ (10%), **8** (10%), Cs_2CO_3 (1.5 equiv.), C_6H_6, 80°C, 40 h	3:1:0
5	**2** (4 equiv.), $Pd_2(dba)_3$ (10%), **9** (10%), Cs_2CO_3 (1.5 equiv.), C_6H_6, 80°C, 12 h	1:8:0
6	**2** (4 equiv.), $Pd(OAc)_2$ (10%), **9** (10%), Cs_2CO_3 (1.5 equiv.), DME, 80°C, 16 h	2:1:0
7	**2** (4 equiv.), $Pd(OAc)_2$ (10%), **9** (10%), K_3PO_4 (1.5 equiv.), C_6H_6, 80°C, 40 h	1:34:0
8	**2** (1 equiv.), $Pd(OAc)_2$ (1%), **9** (1.5%), Cs_2CO_3 (1.5 equiv.), C_6H_6, 80°C, 24 h	1:9:0
9	**2** (4 equiv.), Cs_2CO_3 (1.5 equiv.), C_6H_6, 80°C, 12 h	0:1:0
10	**2** (1.1 equiv.), $Pd(OAc)_2$ (10%), **9** (10%), NaO*t*Bu (1.1 equiv.), C_6H_6, 80°C, 1 h (method B)	4:0:1

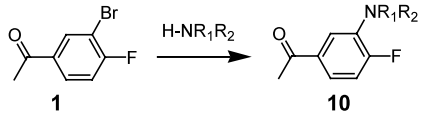
[a] LC–MS ratio of the crude reaction mixture.

reversed when less reagents (piperazine, $Pd(OAc)_2$, and ligand **9**) were applied (entry 8). As a control experiment, **1** was treated with morpholine in the presence of Cs_2CO_3 in benzene under reflux (entry 9), and bromide **4** was formed exclusively. This observation demonstrates the requirement of palladium as a catalyst in the formation of fluoride **3**. Of special note is that all the coupling reactions involving Cs_2CO_3 did not generate any *N*,*N*′-bis-arylpiperazine **5**. We also examined the palladium-catalyzed coupling reaction of **1** with piperazine using NaO*t*Bu as a base (method B, entry 10). The amination proceeded much faster than that with Cs_2CO_3 and provided fluoride **3** and diketone **5** in 75 and 18% yields, respectively. The formation of the bromide **4** was not observed until an excess of piperazine was used.

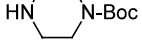
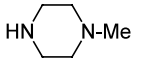
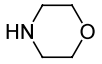
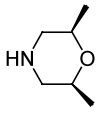
We next applied the above amination conditions to various amines, and the results are shown in Tables 2 and 3. Conditions involving Cs_2CO_3 (method A) worked well with piperazine and morpholine analogs (Table 2), but failed with homomorpholine hydrochloride (Et_3N or additional Cs_2CO_3 was added to neutralize hydrochloride), piperidine, and cyclohexylamine. The coupling reactions with these amines were successfully carried out using NaO*t*Bu as a base (method B), and the amination products (**11**) were obtained in ca. 60% yield (Table 3). The major side products (**12**) in these cases were formed through the palladium-catalyzed α-arylation of the acetyl group.[3] In the case of cyclohexylamine, we also isolated a small amount of bromide **13**.

In a typical experiment of method A, amine (20 mmol) was added to a stirred mixture of acetophenone **1** (5 mmol), $Pd(OAc)_2$ (0.5 mmol), ligand **9** (0.5 mmol) in benzene (8 mL) at room temperature under nitrogen. Cs_2CO_3 (7.5 mmol) was added, and the resulting mixture was heated under reflux until acetophenone had been consumed as judged by LC–MS analysis (usually

Table 2. Amination of 3-bromo-4-fluoro-acetophenone (**1**) using Cs_2CO_3 (method A)

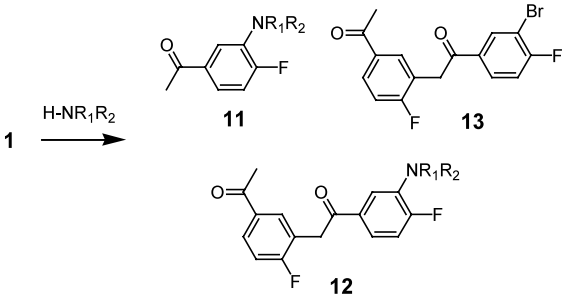


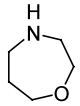
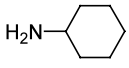
1 **10**

Entry	Amine	**10**[a]
a		81%
b		85%
c		79%
d		63%

[a]isolated yield.

Table 3. Amination of 3-bromo-4-fluoro-acetophenone (**1**) using NaO*t*Bu (method B)



Entry	Amine	**11**[a]	**12**[a]
a	 HCl salt	64%	10%
b		59%	12%
c		58%	8%

[a]isolated yield.

for 16 h). The mixture was cooled to room temperature, diluted with ether, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel eluting with appropriate solvents.

Method B was similar to method A with the exception that 1.1 equiv. NaO*t*Bu was used instead of Cs_2CO_3, 1.1 equiv. amine was added, and the reactions were complete within a couple of hours. In the case of homomorpholine hydrochloride, 2.1 equiv. of NaO*t*Bu was added.

In summary, we have developed a useful and convenient method for the preparation of 3-alkylamino-4-fluoro-acetophenone derivatives through palladium-catalyzed amination reactions.

Acknowledgements

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6. All new compounds have spectral and analytical data in agreement with the indicated structures. Compound **3**: ^{1}H NMR (300 MHz, C_6D_6) δ 0.87 (1H, s), 2.10 (3H, s), 2.64 (4H, m), 2.75 (4H, m), 6.73 (1H, dd, $J=8.4$, 12.3 Hz), 7.08 (1H, m), 7.64 (1H, dd, $J=2.1$, 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 46.2 (2C), 51.8 (2C), 116.1 (d, $J=22.5$ Hz), 118.9 (d, $J=7.5$ Hz), 123.6 (d, $J=7.5$ Hz), 134.0 (d, $J=7.5$ Hz), 140.9 (d, $J=7.5$ Hz), 158.9 (d, $J=255$ Hz), 197.0; HRMS m/z calcd for $C_{12}H_{16}FN_2O$ $(M+H)^+$ 223.1247, found 223.1249. Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (1H, s), 2.46 (3H, s), 3.01 (8H, m), 6.95 (1H, d, $J=8.4$ Hz), 7.78 (1H, dd, $J=1.8$, 8.4 Hz), 8.07 (1H, d, $J=1.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 46.1 (2C), 52.6 (2C), 118.8, 120.1, 128.8, 132.7, 134.5, 155.1, 195.9; HRMS m/z calcd for $C_{12}H_{16}BrN_2O$ $(M+H)^+$ 283.0446, found 283.0442. Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (6H, s), 3.35 (8H, s), 7.12 (2H, dd, $J=8.4$, 12.0 Hz), 7.59 (2H, m), 7.69 (1H, d, $J=6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (2C), 50.4 (4C), 116.2 (2C, d, $J=20$ Hz), 119.0 (2C), 123.9 (2C, d, $J=10$ Hz), 134.0 (2C), 140.2 (2C, d, $J=10$ Hz), 158.8 (2C, d, $J=260$ Hz), 196.8 (2C); HRMS m/z calcd for $C_{20}H_{21}N_2O_2F_2$ $(M+H)^+$ 359.1571, found 359.1556. Compound **10a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.56 (3H, s), 3.06 (4H, t, $J=4.8$ Hz), 3.60 (4H, t, $J=5.1$ Hz), 7.25 (1H, dd, $J=9.0$, 12.0 Hz), 7.56 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 28.5 (3C), 50.5 (2C), 77.4, 80.1 (2C), 116.2 (d, $J=22.5$ Hz), 119.2, 124.0 (d, $J=7.5$ Hz), 134.1, 140.4 (d, $J=7.5$ Hz), 154.8, 158.9 (d, $J=255$ Hz), 196.8; HRMS m/z calcd for $C_{17}H_{22}FN_2O_3$ $(M-H)^-$ 321.1615, found 321.1618. Compound **10b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s), 2.54 (3H, s), 2.57 (4H, t, $J=5.1$ Hz), 3.13 (4H, t, $J=5.1$ Hz), 7.04 (1H, dd, $J=8.4$, 12.3 Hz), 7.51 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 46.2 (2C), 50.4 (2C), 55.2, 116.1 (d, $J=22.5$ Hz), 118.9, 125.5 (d, $J=7.5$ Hz), 134.0 (d, $J=7.5$ Hz), 140.5 (d, $J=15$ Hz), 158.9 (d, $J=255$ Hz), 197.0; HRMS m/z calcd for $C_{13}H_{18}FN_2O$ $(M+H)^+$ 237.1403, found 237.1407. Compound **10c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (3H, s), 3.09 (4H, t, $J=6.4$ Hz), 3.84 (4H, t, $J=4.8$ Hz), 7.05 (1H, dd, $J=8.4$, 12.0 Hz), 7.52 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 50.7 (2C), 66.9 (2C), 116.2 (d, $J=20$ Hz), 118.5 (d, $J=10$ Hz), 123.7 (d, $J=10$ Hz), 134.0, 140.2 (d, $J=10$ Hz), 157.7 (d, $J=250$ Hz), 196.8; HRMS m/z calcd for $C_{12}H_{15}FNO_2$ $(M+H)^+$ 224.1087, found 224.109. Compound **10d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (6H, d, $J=6.0$ Hz), 2.48 (2H, dd, $J=10.4$, 11.2 Hz), 2.57 (3H, s), 3.29 (2H, dd, $J=2.0$, 9.2 Hz), 3.87 (2H, dq, $J=2.4$, 8.4 Hz), 7.08 (1H, dd, $J=8.4$, 12.0 Hz), 7.54 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0 (2C), 26.5, 56.1 (2C), 71.7 (2C), 116.2 (d, $J=30$ Hz), 118.6 (d, $J=10$ Hz), 123.6 (d, $J=10$ Hz), 134.0, 140.0 (d, $J=10$ Hz), 158.7 (d, $J=260$ Hz), 196.9; HRMS m/z calcd for $C_{14}H_{19}FNO_2$ $(M+H)^+$ 252.1400, found 252.1400. Compound **11a**: ^{1}H NMR (400

MHz, $CDCl_3$) δ 2.06 (2H, quintet, $J=5.6$ Hz), 2.55 (3H, s), 3.49 (4H, br t), 3.83 (2H, t, $J=5.6$ Hz), 3.85 (2H, dd, $J=4.8$, 9.2 Hz), 7.04 (1H, dd, $J=8.4$, 12.8 Hz), 7.38 (1H, m), 7.52 (1H, dd, $J=2.0$, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 30.6, 50.8, 54.8, 69.5, 70.8, 116.3 (d, $J=20$ Hz), 117.7, 121.0 (d, $J=10$ Hz), 133.8 (d, $J=10$ Hz), 139.9 (d, $J=10$ Hz), 157.1 (d, $J=250$ Hz), 197.1. Compound **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (2H, m), 1.61 (4H, m), 2.56 (3H, s), 3.05 (4H, t, $J=5.6$ Hz), 7.04 (1H, dd, $J=8.4$, 12.0 Hz), 7.49 (1H, m), 7.61 (1H, d, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 26.0 (2C), 26.5, 51.9 (2C), 115.9 (d, $J=20$ Hz), 119.1 (d, $J=10$ Hz), 123.2 (d, $J=20$ Hz), 133.8 (d, $J=10$ Hz), 141.7 (d, $J=10$ Hz), 158.9 (d, $J=260$ Hz), 197.0. Compound **11c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (4H, m), 1.38 (2H, m), 1.65 (1H, m), 1.75 (2H, m), 2.54 (3H, s), 3.36 (1H, m), 6.98 (1H, dd, $J=8.4$, 11.2 Hz), 7.18 (1H, m), 7.31 (1H, dd, $J=2.0$, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.8, 26.5, 33.2, 51.3, 111.6, 114.3 (d, $J=20$ Hz), 117.7, 134.1, 136.0, 154.5 (d, $J=240$ Hz), 197.5. Compound **12a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (2H, m), 2.58 (3H, s), 3.51 (4H, m), 3.81 (4H, m), 4.32 (2H, s), 7.07 (1H, dd, $J=8.4$, 12.8 Hz), 7.15 (1H, t, $J=9.2$ Hz), 7.47 (1H, m), 7.54 (1H, dd, $J=2.0$, 8.8 Hz), 7.86 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 30.5, 38.6, 50.8, 54.8, 69.5, 70.8, 115.7 (d, $J=20$ Hz), 116.7 (d, $J=30$ Hz), 117.9, 120.6, 122.6, 129.8 (d, $J=10$ Hz), 132.5, 132.8 (d, $J=10$ Hz), 133.6 (d, $J=10$ Hz), 140.0, 157.2 (d, $J=252$ Hz), 164.1 (d, $J=253$ Hz), 194.6, 196.5. HRMS m/z calcd for $C_{21}H_{20}F_2NO_3$ $(M-H)^-$ 372.1411, found 372.1393. Compound **12b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (2H, m), 1.73 (4H, m), 2.57 (3H, s), 3.05 (4H, t, $J=5.6$ Hz), 4.32 (2H, s), 7.08 (1H, dd, $J=8.0$, 12.0 Hz), 7.15 (1H, t, $J=8.0$ Hz), 7.60 (1H, m), 7.62 (1H, m), 7.86 (1H, m), 7.90 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 26.0, 29.7, 38.6, 51.9, 115.7 (d, $J=11$ Hz), 116.2 (d, $J=22$ Hz), 119.5, 122.6 (d, $J=17.5$ Hz), 122.9, 129.8 (d, $J=10$ Hz), 132.6 (d, $J=6.3$ Hz), 132.8 (d, $J=6.3$ Hz), 133.6 (d, $J=3.8$ Hz), 141.8, 159.1 (d, $J=252$ Hz), 164.1 (d, $J=255$ Hz), 194.5, 196.5; HRMS m/z calcd for $C_{21}H_{20}F_2N_2O_2$ $(M-H)^-$ 356.1462, found 356.1461. Compound **12c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (4H, m), 1.37 (2H, m), 1.56 (1H, m), 1.75 (2H, m), 2.02 (2H, m), 2.57 (3H, s), 3.33 (1H, m), 4.32 (2H, s), 7.02 (1H, dd, $J=8.4$, 10.8 Hz), 7.15 (1H, t, $J=8.8$ Hz), 7.29 (1H, m), 7.35 (1H, m), 7.88 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.9, 26.6, 33.3, 38.6, 51.4, 111.8 (d, $J=7.5$ Hz), 114.5 (d, $J=22.5$ Hz), 115.7 (d, $J=22.5$ Hz), 117.3 (d, $J=7.5$ Hz), 122.9 (d, $J=22.5$ Hz), 129.8 (d, $J=15$ Hz), 132.6 (d, $J=7.5$ Hz), 133.1 (d, $J=7.5$ Hz), 133.7 (d, $J=7.5$ Hz), 154.8 (d, $J=248$ Hz), 164.2 (d, $J=248$ Hz), 195.0, 196.6. HRMS m/z calcd for $C_{22}H_{22}F_2NO_2$ $(M-H)^-$ 370.1618, found 370.1630. Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (3H, s), 4.33 (2H, s), 7.17 (1H, t, $J=8.8$ Hz), 7.22 (1H, d, $J=8.0$ Hz), 7.86 (1H, dd, $J=2.0$, 6.8 Hz), 7.92 (1H, m), 7.98 (1H, m), 8.04 (1H, m), 8.25 (1H, dd, $J=2.0$, 6.4 Hz).