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Microwave mediated reduction of heterocycle and fluorine containing nitroaromatics with $Mo(CO)_6$ and DBU

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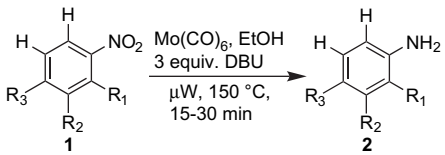
ABSTRACT

Heterocycle containing nitroaromatics were reduced by $Mo(CO)_6$ and DBU in EtOH under microwave irradiation within 15 min. Under the same conditions, 4-fluoronitrobenzene was reduced to 4-fluoroaniline, whereas 2-chloro-1-fluoro-4-nitrobenzene afforded a mixture of 3-chloro-4-fluoroaniline and 3-chloro-4-ethoxyaniline. The extent of the competing S_NAr/reduction process could be influenced by the nature of the solvent, with *t*-BuOH the inert solvent of choice. The latter was used as solvent for S_NAr/reductions of 2-chloro-1-fluoro-4-nitrobenzene with *S*-nucleophiles to yield 3-chloro-4-mercaptoanilines.

1. Introduction

The microwave mediated reduction of nitroaromatics **1** using stoichiometric $Mo(CO)_6$ and DBU (1,8-diazabicyco[5.4.0]undec-7-ene) was recently reported by us to be a convenient, rapid route to a host of anilines **2** and is typically performed in EtOH, at 150 °C within 15 min (Scheme 1). This method tolerates a variety of functionalities, including halide, ketone, nitrile, carboxamide, vinyl, alcohol, and was found to operate for one heterocyclic substrate; 5-aminoquinoline was synthesised from its nitro precursor in excellent yield (Table 1, entry 3, vide infra).[1] Consequently, we wished to apply this protocol to the synthesis of a wider range of amines by subjecting a series of heterocycle containing nitroaromatics to our standard reduction conditions.



Scheme 1.

2. Results and discussion

The reduction process works well for indoline analogues, isomeric nitro-quinoline and -isoquinoline derivatives as well as piperazine-containing nitrobenzenes (Table 1) including the amide **3f**.[2] An *N*-arylated imidazole **3g** was reduced in good yield to the corresponding aniline **4g**[3] (entry 7), and brominated nitropyridine and indole derivatives **3h** and **3i** were reduced in good yields (to **4h**[4] and **4i**, entries 8 and 9, respectively). In line with our earlier observations, a halide group was tolerated.[1]

However, not all nitro substrates were reduced and we obtained uncharacterised products for the attempted reduction of 5-nitroindazole, 6-nitrochromone, 2-bromo-5-nitrothiazole (with pungent odour formation), 5-nitroisatin, 4-nitroimidazole and 2-furoic acid methyl ester. Moreover, the attempted reduction of the aliphatic nitro compound 2-(2-nitroethoxy)tetrahydropyran was unsuccessful.

The reduction protocol is also compatible with palladium-catalysed coupling reactions. For example, the Suzuki–Miyaura coupling product **6**,[6] which contains a basic piperazine moiety as well as a potentially labile Boc protecting group, was reduced to afford biphenylamine **7**, albeit in poor yield, and purified by solid phase extraction (SPE). The reduction of the Sonogashira product[7] **9** furnished the aniline **10** gratifyingly with concomitant loss of the trimethylsilyl protecting group (Scheme 2).

Substituted anilines, including **10**, constitute important precursors to several kinase inhibitors.[8–10] A variety of substituents, including ethynyl, halides, ethers and thioethers are tolerated in

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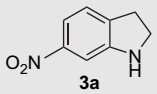
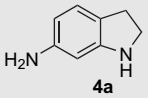
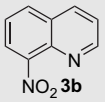
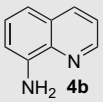
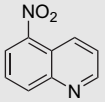
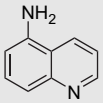
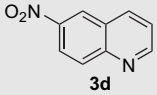
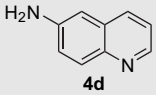
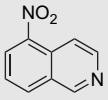
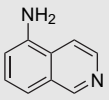
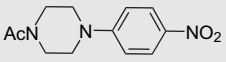
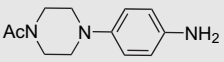
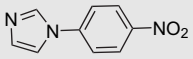
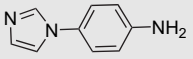
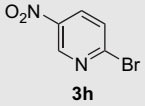
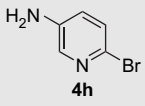
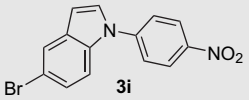
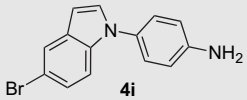
Table 1
Reduction of nitro containing heterocycles

Entry[a]	Starting material	Product (% isolated yield)	Yield (%)
1	 **3a**	 **4a**	65
2	 **3b**	 **4b**	85
3	 **3c**	 **4c**	92[b]
4	 **3d**	 **4d**	87
5	 **3e**	 **4e**	81
16	 **3f**	 **4f**	66
7	 **3g**	 **4g**	67
8	 **3h**	 **4h**	72
9	 **3i**	 **4i**	89

[a] Reaction conditions: 0.5 mmol scale (1.5 mmol DBU); 150 °C, 15 min. Products purified by chromatography (SiO_2) and characterised by ^1H, ^{13}C NMR spectroscopy and HRMS.
[b] From Ref. 1.

the hydrophobic pocket binding region of the kinase receptor, which, inter alia, can influence the biological profile of the ligand (Fig. 1).[11] A number of these important anilines can be derived from the reduction of 2-chloro-1-fluoro-4-nitrobenzene **11b** or from a nucleophilic displacement of fluoride in **11b** prior to the reduction. A further extension of this work led us to investigate the reduction of fluoronitrobenzenes **11a** and **11b** using the standard conditions with the aim of investigating potential concomitant reduction/S_NAr processes (Table 2).

The reduction of 4-fluoronitrobenzene **11a** yielded the aniline **12a** in 57% yield (entry 1). For the corresponding reaction of **11b** we observed reduction of the nitro group affording the aniline **12b**, and the ether substituted aniline **12b′**, signifying indeed that a reduction and substitution process can take place (entry 2). The latter probably results from an initial S_NAr reaction of **11b** with the solvent followed by the reduction process; a similar substitution product was not observed in the ^1H NMR spectrum of the crude reaction mixture of **12a**. Increasing the reaction time led to a higher yield of the aniline **12b** with no significant change in the yield of the substitution product **12b′** (entry 3).

We next wished to investigate the use of sterically hindered, less reactive, alcohols such as *i*-PrOH and *t*-BuOH, in order to deter the competing S_NAr reaction of **11b** with the solvent. Hence, when performing the reduction in *i*-PrOH, the aniline **12b** was obtained in 56% yield along with traces of the S_NAr/reduction product **12b″** (entry 4). The corresponding reaction in the more hindered *t*-BuOH furnished **12b** in 52% yield and, as expected, no substitution/reduction product was obtained (entry 5).[12]

We finally wished to perform one-pot fluoride displacement/nitro reductions employing strong nucleophiles with the aim of achieving the S_NAr reaction prior to the reduction, all within 15 min. The thioether-containing aniline **13a**[13] was formed in excellent yield (Table 2, entry 6) using sodium thiomethoxide as nucleophile in *t*-BuOH. With thiols, poorer yields were obtained and the reactions appeared to be less selective. Moreover, changing the stoichiometry by using an excess of thiol, adding extra base or changing the reaction time did not improve the yield of product. The aniline **13b** was formed in only 24% yield (entry 7) and **13c** was synthesised in 35% yield after purification (entry 8). Carrying out the reaction stepwise, i.e., performing the S_NAr initially (to give **14**[8]), followed by the reduction of **14**, only slightly improved the yield of **13c** (44% opposed to 35%, Table 2, entries 8 and 9).

3. Conclusion

We have described a convenient chemoselective synthetic protocol for the microwave mediated formation of a variety of anilines, including a series of *N*-heterocycle containing anilines **4**, starting from their nitro precursors. The fluoronitrobenzenes **11a** and **11b** underwent a series of competing S_NAr/reduction processes with a host of thiol or thiolate and alcohol nucleophiles, affording the anilines **12** and **13**, with known or potential uses as precursors to kinase inhibitors. Further work is in progress to extend this methodology towards the synthesis of further compounds of biological interest and will be reported in due course.

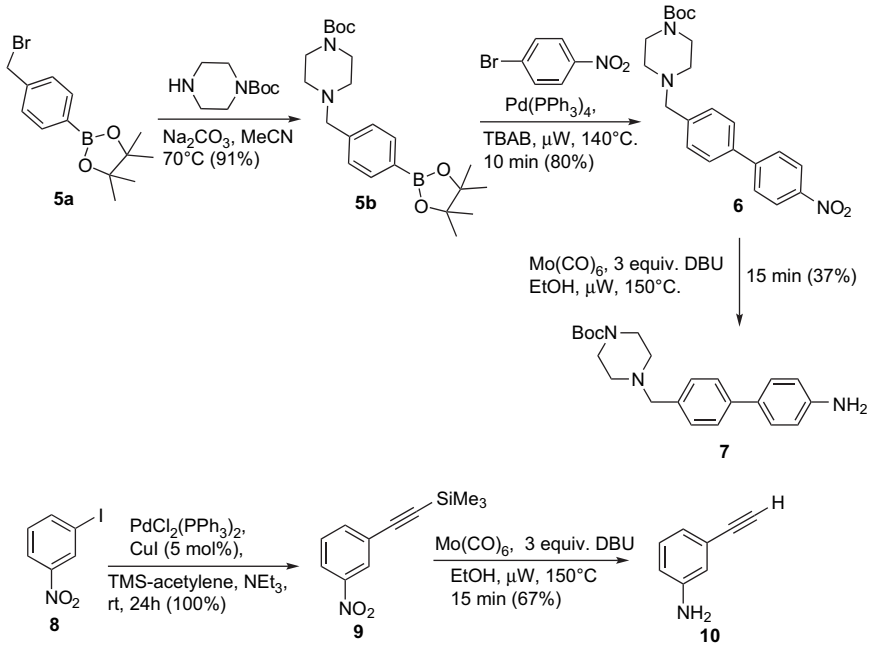
4. Experimental

4.1. General

Starting materials were purchased from commercial sources (Sigma–Aldrich, Fisher, Fluorochem, Frontier Scientific) and used without further purification. All reactions were carried out in air, and commercial grade solvents and materials were used except where specified. NMR spectra were measured on a Jeol EX270 spectrometer at 270 MHz (^1H) and 75 MHz (^{13}C) in $CDCl_3$. Microwave reactions were performed in a CEM Discover unit. Elemental analyses were performed on a CE Instruments apparatus.

*4.1.1. 5-Bromo-1-(4-nitrophenyl)-1H-indole **3i***

5-Bromoindole (1.96 g, 10.00 mmol) was stirred with sodium hydride (600 mg, 15.00 mmol, 60% suspension in mineral oil) in dry DMF (30 mL) for 0.5 h. Thereafter, 1-fluoro-4-nitrobenzene (1.41 g, 10.00 mmol) was added and the mixture was stirred overnight. Brine (20 mL) and ethyl acetate (30 mL) were added and the separated organic layer was washed with further brine (2×10 mL) and water (1×20 mL). After drying ($MgSO_4$), the organics were concentrated in vacuo to ca. 5 mL and the addition of hexane led to the formation of an orange precipitate, which was collected by filtration and dried in air. Yield 2.07 g (65%); orange solid. Mp 147–150 °C. (Found: C, 53.14; H, 2.83; N, 8.53. $C_{14}H_9BrN_2O_2$ requires C, 53.02; H, 2.86; N, 8.83) ^1H NMR ($CDCl_3$) δ 8.39 (2H, d, J=8.5 Hz), 7.81 (1H, d, J=8.5 Hz), 7.66 (2H, m), 7.62 (1H, m), 7.37 (2H, m), 6.69 (1H, m). ^{13}C NMR ($CDCl_3$) δ 145.4, 144.7, 133.9, 131.7, 128.3, 126.2, 125.5,



Scheme 2.

124.1, 123.5, 114.6, 111.8, 105.4. IR (KBr disk, cm^{-1}) 3200, 1590, 1508, 1450, 1330, 850. HRMS: *m*/*z* calcd for $C_{14}H_9BrN_2O_2$ (M^+): 315.9842, found: 315.9846.

4.2. General conditions for the reduction of heterocycle containing nitroarenes

The nitroarene (0.5 mmol), $Mo(CO)_6$ (132 mg, 0.5 mmol), DBU (228 μl, 1.5 mmol) and ethanol (5 mL) were charged into a microwave tube with a stirring bar. The tube was sealed and the temperature was ramped until 150 °C, then kept at this temperature for 15 min. After cooling, the mixture was concentrated under reduced pressure [Warning! The solvent is heated to a very high temperature, well above its boiling point, in a sealed apparatus under a suitable fume hood and after the reaction, should be left to cool to around room temperature before opening the vessel. The reaction power was set at 300 W for the initial power input and this value usually drops once the required temperature has been reached.]. After purification by column chromatography (typically using a gradient of neat dichloromethane to 10:1 dichloromethane/acetone) pure product was obtained.

4.2.1. 2,3-Dihydro-1H-indole-6-amine ***4a***

Black oil. Yield: 44 mg (65%). ^1H NMR ($CDCl_3$) δ 6.88 (1H, d), 6.02 (2H, m), 3.52–3.46 (5H, m), 2.90 (2H, t, *J*=7.6 Hz). ^{13}C NMR ($CDCl_3$)

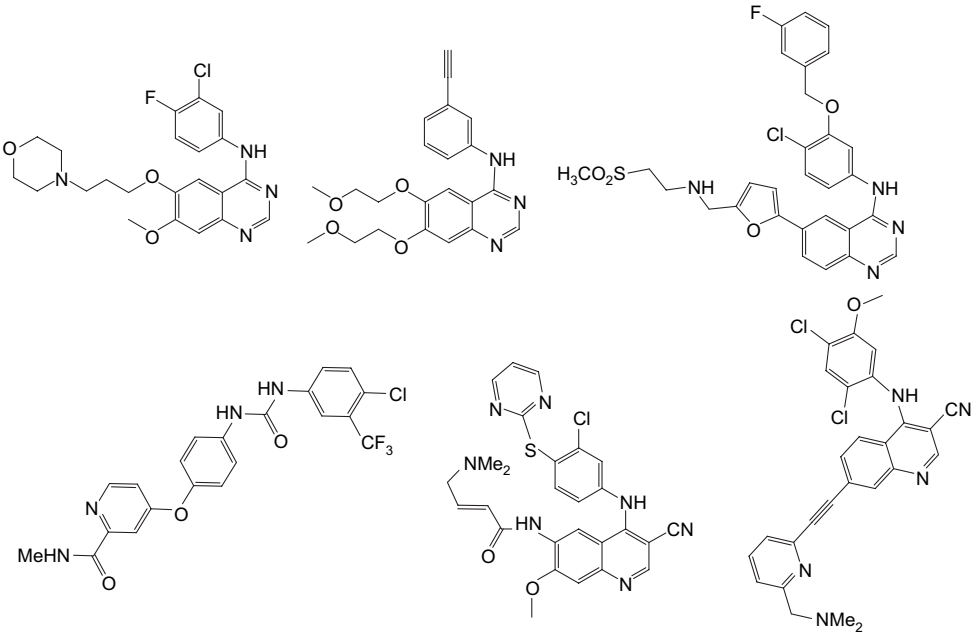
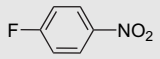
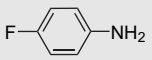
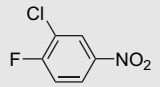
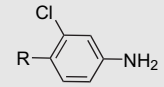
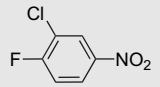
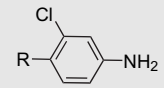
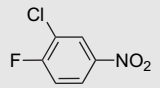
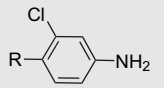
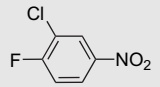
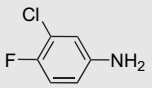
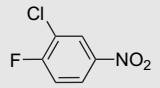
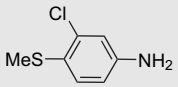
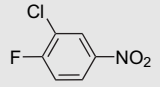
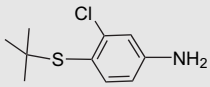
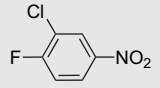
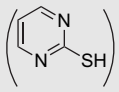
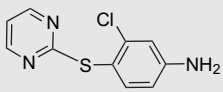
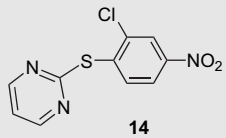
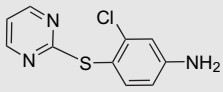


Figure 1.

Table 2
S_NAr/nitro reduction versus nitro reduction in fluorinated nitroaromatics[a]

Entry	Starting material	Solvent (nucleophile, where applicable)	Product	Yield (%)
1	 **11a**	EtOH	 **12a**	57
2	 **11b**	EtOH	 **12b**: R= F. **12b'**: R=OEt	**12b** (41) **12b′** (13)
3[b]	 **11b**	EtOH	 **12b**: R= F. **12b'**: R=OEt	**12b** (79) **12b′** (14)
4	 **11b**	*i*-PrOH	 **12b**: R= F. **12b''**: R=O*i*-Pr	**12b** (56) **12b″** (10)
5	 **11b**	*t*-BuOH	 **12b**	52
6	 **11b**	*t*-BuOH (NaSMe)	 **13a**	90
7	 **11b**	*t*-BuOH (HS*t*-Bu)	 **13b**	24
8	 **11b**	*t*-BuOH 	 **13c**	35
9	 **14**	*t*-BuOH	 **13c**	44

[a] 0.5 mmol scale (1.5 mmol DBU); 150 °C, 15 min. Products purified by chromatography (SiO_2) and characterised by ^1H, ^{13}C NMR spectroscopy, MS ands/or HRMS.
[b] As for conditons described in footnote a, but 30 min.

δ 152.9, 146.2, 125.0, 119.7, 105.6, 97.5, 47.8, 29.1. IR (neat, cm^{-1}) 3480, 3008, 1619, 1215, 753. HRMS: *m*/*z* calcd for $C_8H_{10}N_2$ (MH^+): 135.0917, found: 135.0919.

4.2.2. 8-Aminoquinoline ***4b***

Grey solid. Yield: 62 mg (85%).[5] Mp 62–65 °C (lit. 60–65 °C).[14] ^1H NMR ($CDCl_3$) δ 8.75 (1H, d, *J*=2.1 Hz), 8.05 (1H, dd, *J*=2.1, 6.7 Hz), 7.36 (2H, m), 7.15 (1H, d, *J*=6.7 Hz), 6.93 (1H, d, *J*=6.7 Hz), 5.14 (2H, br s). HRMS: *m*/*z* calcd for $C_9H_9N_2$ (MH^+): 145.0760, found: 145.0759.

4.2.3. 5-Aminoquinoline ***4c***

Brown solid. Yield: 66 mg (92%). Mp 107–110 °C (lit. 107–109 °C).[14] ^1H NMR ($CDCl_3$) δ 8.84 (1H, d, *J*=2.7 Hz), 8.14 (1H, d, *J*=2.7 Hz), 7.56 (1H, d, *J*=5.4 Hz), 7.47 (1H, d, *J*=5.4 Hz), 7.29 (1H, m), 6.77 (1H, d, *J*=5.4 Hz), 4.19 (2H, br s). HRMS: *m*/*z* calcd for $C_9H_9N_2$ (MH^+): 145.0760, found: 145.0759.

4.2.4. 6-Aminoquinoline ***4d***

Yellow solid. Yield: 63 mg (87%).[5] Mp 110–115 °C (lit. 115–119 °C).[14] (Found: C, 74.92; H, 5.67. $C_9H_8N_2$ requires C, 74.98; H, 5.59) ^1H NMR ($CDCl_3$) δ 8.62 (1H, m), 7.85 (2H, m), 7.24 (1H, m), 7.13 (1H, dd, *J*=5.4, 2.7 Hz), 6.85 (1H, d, *J*=2.9 Hz), 3.97 (2H, br s). HRMS: *m*/*z* calcd for $C_9H_9N_2$ (MH^+): 145.0760, found: 145.0760.

4.2.5. Isoquinoline-5-amine ***4e***

Brown solid. Yield: 68 mg (81%). Mp 125–128 °C (lit. 128 °C).[14] (Found: C, 74.93; H, 5.61; N, 19.28. $C_9H_8N_2$ requires C, 74.98; H, 5.59;

N, 19.43) ^{1}H NMR ($CDCl_3$) δ 9.12 (1H, s), 8.43 (1H, d, J=6.1 Hz), 7.52 (1H, d, J=6.1 Hz), 7.34 (2H, t, J=4.0 Hz), 6.88 (1H, m), 4.24 (2H, br s). ^{13}C NMR ($CDCl_3$) δ 152.8, 141.8, 141.3, 129.3, 127.6, 125.8, 117.7, 114.1, 112.9. IR (KBr disk, cm^{-1}) 3372, 3196, 1636, 1582, 1494, 1445, 1292, 1240, 797. HRMS: m/z calcd for $C_9H_9N_2$ (MH^+): 145.0760, found: 145.0759.

4.2.6. 4-(4-Acetylpiperazin-1-yl)aniline **4f**

Dark oil. Yield: 72 mg (66%). ^{1}H NMR ($D_2O/CDCl_3$) δ 6.78 (2H, d, J=8.6 Hz), 6.62 (2H, d, J=8.6 Hz), 3.73 (2H, m), 3.56 (2H, m), 2.97 (4H, m), 2.12 (3H, s). ^{13}C NMR ($CDCl_3$) δ 168.9, 143.9, 140.8, 119.3, 119.2, 116.0, 114.8, 51.4, 51.0, 46.4, 41.5, 21.3. IR (neat, cm^{-1}) 3413, 3346, 1628, 1513, 1450, 1272, 1224, 1142, 997, 820. HRMS: m/z calcd for $C_{12}H_{18}N_3O$ (MH^+): 220.1444, found: 220.1444.

4.2.7. 4-(1H-Imidazol-1-yl)aniline **4g**

Pale yellow solid. Yield: 54 mg (67%). Mp 136–141 °C (lit. 143–147 °C).[14] ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, s), 7.11 (3H, m), 7.06 (1H, d, J=8.6 Hz), 6.65 (2H, dd, J=8.6, 7.0 Hz), 3.75 (2H, br s). ^{13}C NMR ($CDCl_3$) δ 146.0, 135.8, 129.7, 128.8, 123.2, 118.8, 115.5. IR (KBr disk, cm^{-1}) 3343, 3186, 3107, 1656, 1606, 1519, 1270, 1101, 1057, 905, 826, 664. HRMS: m/z calcd for $C_9H_{10}N_3$ (MH^+): 160.0869, found: 160.0867.

4.2.8. 6-Bromopyridine-3-amine **4h**

Grey solid. Yield: 62 mg (72%). Mp 75–80 °C (lit. 76 °C).[14] (Found: C, 35.09; H, 2.95; N, 15.85. $C_5H_5BrN_2$ requires C, 34.71; H, 2.91; N, 16.19) ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, d, J=2.9 Hz), 7.19 (1H, d, J=8.4 Hz), 6.87 (1H, dd, J=8.4, 2.9 Hz), 3.58 (2H, br s). ^{13}C NMR ($CDCl_3$) δ 142.2, 137.1, 129.5, 127.9, 124.8. IR (KBr disk, cm^{-1}) 3362, 3186, 1631, 1459, 1288, 827. HRMS m/z calcd for C_5H_6BrN (MH^+): 172.9709, found: 172.9712.

4.2.9. 4-(5-Bromo-1H-indol-1-yl)aniline **4i**

Brown oil. Yield: 63 mg (89%). ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, s), 7.28–7.18 (5H, m), 6.78 (2H, d, J=8.4 Hz), 6.55 (1H, d, J=3.4 Hz), 3.79 (2H, br s). ^{13}C NMR ($CDCl_3$) δ 145.5, 135.1, 130.4, 130.2, 129.5, 125.9, 124.7, 123.2, 115.6, 113.0, 111.9, 101.9. IR (neat, cm^{-1}) 3431, 3320, 3215, 1626, 1518, 1457, 1260, 1116, 832, 714. HRMS m/z calcd for $C_{14}H_{11}BrN_2$ (M^+); 286.0100, found: 286.0101.

4.2.10. 2-[2-(4-(Boc)piperazinylmethyl)bromophenyl]-4,4,5,5-tetramethyl-1,3-dioxolane **5b**

2-[2-(Bromomethyl) bromophenyl]-4,4,5,5-tetramethyl-1,3-dioxolane **5a** (503 mg, 2.33 mmol), 1-(Boc)piperazine (450 mg, 2.42 mmol) and Na_2CO_3 (265 mg, 2.50 mmol) were heated in acetonitrile (20 mL) at 80 °C for 3 h. After cooling, the reaction mixture was filtered. To the filtrate was added an equal amount of CH_2Cl_2/hexane (20 mL) and the white precipitate was collected by filtration and was discarded. The filtrate was concentrated in vacuo to give crude **5b**. Yellow oil, used as such. Yield: 845 mg (91%). ^{1}H NMR ($CDCl_3$) δ 7.40–7.24 (4H, m), 3.48 (2H, s), 3.39 (4H, m), 2.35 (4H, s), 1.42 (9H, s), 1.32 (12H, s).

4.2.11. 4-Boc-1-[(4′-nitrobiphenyl-4-yl)methyl]piperazine **6**

In a 5 mL microwave tube were placed **5b** (467 mg, 1.16 mmol), 1-bromo-4-nitrobenzene (222 mg, 1.10 mmol), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), aqueous Na_2CO_3 (2.0 M, 1 mL), toluene (2 mL), ethanol (2 mL) and a magnetic stir bar. The vessel was sealed and placed in the microwave cavity. An initial microwave irradiation of 300 W was used, the temperature being ramped from room temperature to 140 °C. Once 140 °C was reached, the reaction vessel was held at this temperature for 10 min.[15] After cooling, the reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was purified by flash chromatography with CH_2Cl_2/acetone, (10:1). Yellow solid. Yield: 369 mg (80%). Mp 130–132 °C. (Found: C, 66.17; H, 6.92. $C_{22}H_{27}N_3O_4$ requires C, 66.48; H, 6.85) ^{1}H NMR ($CDCl_3$) δ 8.21 (2H, dd, J=8.6, 1.8 Hz), 7.66 (2H, dd J=8.6, 1.8 Hz), 7.52 (2H, dd, J=8.1 Hz), 7.40 (2H, dd, J=8.1 Hz,), 3.50 (2H, s), 3.39 (4H, t, J=4.8 Hz), 2.34 (4H, t, J=4.8 Hz), 1.41 (9H, s). ^{13}C NMR ($CDCl_3$) δ 154.8, 148.8, 148.3, 139.7, 138.6, 136.6, 130.1, 128.8, 128.6, 123.7, 79.4, 62.3, 51.8, 40.8, 28.7. IR (KBr disk, cm^{-1}) 2970, 1686, 1508, 1340, 1244, 1166, 990. HRMS m/z calcd for $C_{22}H_{28}N_3O_2$ (MH^+): 398.2074, found: 398.2070.

4.2.12. 4′-Boc-(piperazin-1-ylmethyl)biphenyl-4-amine **7**

Compound **6** (198 mg, 0.5 mmol), $Mo(CO)_6$ (132 mg, 0.5 mmol) and DBU (228 μL, 1.5 mmol) were combined with ethanol (5 mL) and placed in a microwave tube and irradiated at 150 °C (initial power setting of 300 W) for 30 min. After cooling, the reaction mixture was concentrated and purified using an SCX column; elution with MeOH removed impurities. Elution with methanol/ammonia yielded the product **7**. Yellow oil. Yield: 66 mg (37%). ^{1}H NMR ($CDCl_3$) δ 7.48–7.32 (6H, m), 6.77 (2H, d, J=8.4 Hz), 3.50 (2H, s), 3.41 (6H, m), 2.41 (4H, d, J=4.9 Hz), 1.23 (9H, s). ^{13}C NMR ($CDCl_3$) δ 152.2, 143.0, 137.5, 133.1, 129.6, 129.4, 128.6, 126.9, 126.0, 125.8, 125.3, 123.6, 112.8, 74.9, 60.2, 50.3, 40.0, 25.8. IR (neat, cm^{-1}) 3047, 2970, 1681, 1498, 1346, 1165, 998, 864, 755. HRMS: m/z calcd for $C_{22}H_{29}N_3O_2$ (M^+): 367.2254, found: 367.2258.

4.2.13. 1-(2-Trimethylsilyl)ethynyl-3-nitrobenzene **9**

This was made crude, in quantitative yield, based on a related synthesis,[7a] on a 2 mmol scale, and used as such for the synthesis of **10**. ^{1}H NMR ($CDCl_3$) δ 8.29 (1H, d, J=8.0 Hz), 8.18 (1H, m), 7.72 (1H, m), 7.46 (1H, t), 0.26 (9H, s).

4.2.14. 3-Ethynylaniline **10**

This was synthesised from **9** using the general conditions for the reduction of heterocycle containing nitroarenes as stated above. Dark brown oil. Yield: 42 mg (67%). ^{1}H NMR ($CDCl_3$) δ 7.08 (1H, t, J=8.0 Hz), 6.89 (1H, dt, J=8.0, 1.0 Hz), 6.79 (1H, d, J=2.0 Hz), 6.65 (1H, dd, J=8.0, 2.0 Hz), 3.65 (2H, br s), 3.05 (1H, s). ^{13}C NMR ($CDCl_3$) δ 146.3, 129.3, 122.8, 122.6, 118.4, 115.9, 83.9, 76.5 (concealed by $CDCl_3$).[16] IR (neat, cm^{-1}) 3442, 3365, 3287, 3009, 1676, 1619, 1349, 1219, 758. HRMS: m/z calcd for C_8H_8N (MH^+): 118.0651, found: 118.0652.

4.2.15. 4-Fluoroaniline **12a**

Red oil. Yield: 34 mg (57%).[5] ^{1}H NMR ($CDCl_3$) δ 6.80 (2H, m), 6.59 (2H, m), 3.51 (2H, br s). HRMS: m/z calcd for C_6H_6FN (M^+): 111.0479, found: 111.0478.

4.2.16. 3-Chloro-4-fluoroaniline **12b**

The standard conditions were employed, except using 30 min reaction time. Black oil. Yield: 57 mg (79%).[5] ^{1}H NMR ($CDCl_3$) δ 6.86 (1H, m), 6.66 (1H, m), 6.49 (1H, m), 3.57 (2H, br s). HRMS: m/z calcd for C_6H_5ClFN (M^+): 146.0167, found: 146.0167.

4.2.17. 3-Chloro-4-ethoxyaniline **12b′**

Brown oil. Yield: 12 mg (14%). ^{1}H NMR ($CDCl_3$) δ 6.77 (1H, s), 6.73 (1H, m), 6.52 (1H, dd, J=8.4, 2.9 Hz), 4.03 (2H, q, J=7.3 Hz), 3.44 (2H, br s), 1.43 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 147.4, 140.8, 124.1, 117.2, 116.2, 114.2, 65.9, 14.9. IR (KBr disk, cm^{-1}) 3440, 3362, 1616, 1498, 1224, 1052. HRMS: m/z calcd for $C_8H_{11}ClNO$ (MH^+): 172.0524, found: 172.0526.

4.2.18. 3-Chloro-4-isopropoxyaniline **12b″**

Pale yellow oil. Yield: 9 mg (10%). ^{1}H NMR ($CDCl_3$) δ 6.80 (1H, d, J=8.4 Hz), 6.71 (1H, d, J=2.9 Hz), 6.49 (1H, dd, J=8.4, 2.9 Hz), 4.33 (1H, sept, J=5.8 Hz), 3.48 (2H, br s), 1.31 (6H, d, J=5.8 Hz). ^{13}C NMR ($CDCl_3$) δ 146.4, 141.6, 126.1, 120.3, 116.8, 114.3, 73.9, 22.2. IR (KBr disk, cm^{-1}) 3460, 3377, 1626, 1499, 1052. HRMS: m/z calcd for $C_9H_{12}ClNO$ (M^+): 185.0602, found: 185.0602.

*4.2.19. 3-Chloro-4-(methylsulfanyl)aniline **13a***

The method employed was as for the synthesis of **13c** except that sodium thiomethoxide was used as the nucleophile. Brown solid. Yield: 159 mg (90%). Mp 65–70 °C. (Found: C, 48.71; H, 4.65; N, 7.79. C_7H_8ClNS requires C, 48.41; H, 4.64; N, 8.07) ^{1}H NMR ($CDCl_3$) δ 7.08 (1H, d, J=8.4 Hz), 6.68 (1H, d, J=2.2 Hz), 6.48 (1H, m), 3.68 (2H, br s), 2.35 (3H, s). ^{13}C NMR ($CDCl_3$) δ 145.9, 135.3, 131.1, 123.9, 115.9, 114.1, 17.6. IR (KBr disk, cm^{-1}) 3365, 2960, 1594, 1164. HRMS: m/z calcd for C_7H_9ClNS (MH^+): 174.0139; found: 174.0138.

*4.2.20. 4-(tert-Butylsulfanyl)-3-chloroaniline **13b***

The method employed was as for the synthesis of **13c** except that *tert*-butylmercaptan was used as the nucleophile. Black oil. Yield: 26 mg (24%). ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, d, J=8.4 Hz), 6.78 (1H, d, J=2.1 Hz), 6.48 (1H, m), 3.82 (2H, br s), 1.25 (9H, s). ^{13}C NMR ($CDCl_3$) δ 148.2, 142.0, 141.0, 119.4, 115.8, 113.3, 47.7, 30.8. IR (KBr disk, cm^{-1}) 3461, 2961, 1622, 1594, 1023. ESI-MS: m/z (%) 215 (10, M^+), 159 (60, M−isobutene). HRMS: m/z calcd for $C_{10}H_{14}ClNS$ (M^+) 215.0530, found: 215.0530.

*4.2.21. 3-Chloro-4-(pyrimidin-2-ylsulfanyl)aniline **13c***

3-Chloro-4-fluoronitrobenzene (88 mg, 0.5 mmol), $Mo(CO)_6$ (132 mg, 0.5 mmol), DBU (228 μl, 1.5 mmol), 2-mercaptopyrimidine (66 mg, 0.5 mmol) and *tert*-butanol (5 mL) were charged into a microwave tube. A stirring bar was added. The tube was sealed and the mixture was heated in a microwave at 150 °C (initial power set at 300 W) for 15 min, then allowed to cool to room temperature. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (pure dichloromethane to 5:1 dichloromethane/acetone). White solid. Yield: 42 mg (35%). Mp 135–140 °C. (Found: C, 50.23; H, 3.39; N, 17.14. $C_{10}H_8ClN_3S$ requires C, 50.53; H, 3.39; N, 17.68) ^{1}H NMR ($CDCl_3$) δ 8.44 (2H, d, J=4.7 Hz), 7.43 (1H, d, J=8.4 Hz), 6.92 (1H, t, J=4.7 Hz), 6.79 (1H, d, J=2.2 Hz), 6.57 (1H, dd, J=8.4, 2.2 Hz), 3.97 (2H, br s). ^{13}C NMR ($CDCl_3$) δ 172.6, 157.7, 157.4, 149.3, 140.8, 138.6, 116.7, 116.1, 113.8. IR (KBr disk, cm^{-1}) 3346, 3230, 1652, 1595, 1556, 1372, 1181. HRMS: m/z calcd for $C_{10}H_9ClN_3S$ (MH^+): 238.0200, found: 238.0202.

*4.2.22. 3-Chloro-4-(pyrimidin-2-ylsulfanyl)aniline (**13c**)*

An alternative synthesis from **14**[8] using the standard conditions for the reduction of heterocycle containing nitroarenes, in EtOH, as stated above, led to a 44% yield of **13c**.

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References and notes

1. Spencer, J.; Nazira, A.; Patel, H.; Rathnam, R. P.; Verma, J. *Synlett* **2007**, 2557.
2. Stefane, B.; Cernigoj, U.; Kocevar, M.; Polanc, S. *Tetrahedron Lett.* **2001**, *42*, 6659.
3. (a) Smallheer, J. M.; Alexander, R. S.; Wang, J.; Wang, S.; Nakajima, S.; Rossi, K. A.; Smallwood, A.; Barbera, F.; Burdick, D.; Luettgen, M. J.; Knabb, M. R.; Wexler, R. R.; Jadhav, K. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5263; (b) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435.
4. Cañibano, V.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; Carreño, M. C.; González, G.; García-Ruano, J. L. *Synthesis* **2001**, 2175.
5. ^{1}H and ^{13}C spectra of **4b**–**4e** and **12a**, **12b** correspond to the literature values (Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*, 1st ed.; Aldrich Chemical: USA, 1993).
6. (a) For our earlier work describing substitution reactions on a preformed arylboronate, see Spencer, J.; Burd, A. P.; Adatia, T.; Goodwin, C. A.; Merette, S. A. M.; Scully, M. F.; Deadman, J. J. *Tetrahedron* **2002**, *58*, 1551; (b) Holland, R.; Spencer, J.; Deadman, J. J. *Synthesis* **2002**, 2379.
7. (a) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280; (b) Related ethynylanilines can be synthesized directly from an iodoaniline and a suitable acetylene, see Melissarist, A. P.; Litt, M. H. *J. Org. Chem.* **1994**, *59*, 5818.
8. Berger, D.; Dutia, M.; Powell, D.; Wu, B.; Wissner, A.; Boschelli, D. H.; Brawner Floyd, M.; Zhang, N.; Torres, N.; Levin, J.; Du, X.; Wojciechowicz, D.; Discafani, C.; Kohler, C.; Kim, S. C.; Feldberg, L. R.; Collins, K.; Mallon, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3031.
9. Wu, B.; Barrios Sosa, A. C.; Boschelli, D. H.; Boschelli, F.; Honores, E. E.; Golas, J. M.; Powell, D. W.; Wang, Y. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3993.
10. Tsou, H. R.; Overbreek-Klumpers, E. G.; Hallet, W. A.; Reich, M. F.; Brawner Floyd, M.; Johnson, B. D.; Michalak, R. S.; Nilakantan, R.; Discafani, C.; Golas, J.; Rabindran, S. K.; Shen, R.; Shi, X.; Wang, Y. F.; Upeclacis, J.; Wissner, A. *J. Med. Chem.* **2005**, *48*, 1107.
11. Reviews: (a) Collins, I.; Workman, P. *Curr. Signal Transduct. Ther.* **2006**, *1*, 13; (b) Levitzki, A. *Acc. Chem. Res.* **2003**, *36*, 462; (c) Moy, B.; Kirkpatrick, P.; Kar, S.; Goss, P. *Nat. Drug Discov. Rev.* **2007**, *6*, 431.
12. Increasing the size of the nucleophile in related reductions reduces competing S_NAr reactions, see Bentley, J. M.; Davidson, J. E.; Duncton, M. A. J.; Giles, P. J.; Pratt, R. M. *Synth. Commun.* **2004**, *34*, 2295.
13. Howard, H. R., Jr.; Adam, M. D.; Andrews, M. D.; Elliott, M. L.; Gymer, G. E.; Hepworth, D.; Middleton, D. S.; Stobie, A. U.S. Patent 6,610,747, 2003.
14. Compared with the values reported for commercial samples from Sigma–Aldrich or with data from *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, NY, 1982.
15. Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888.
16. Bosch, E.; Jeffries, L. *Tetrahedron Lett.* **2001**, *42*, 8141.