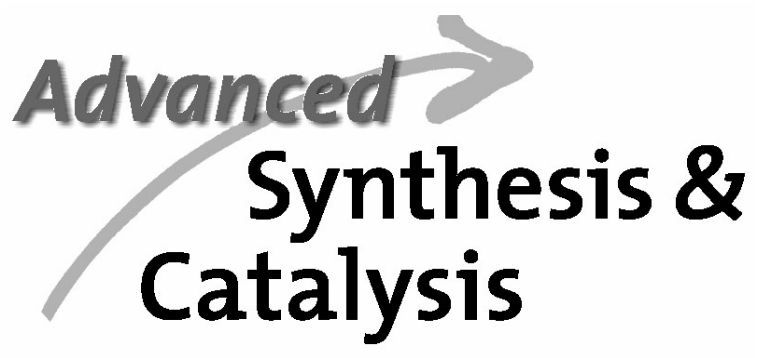

Supporting Information

Applicability Aspects of Transition Metal Catalyzed Aromatic Amination Protocols in Medicinal Chemistry

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Supporting Information

All reference citations refer to the References and Notes section of the main text except for those marked with "S".

Challenging Substrates for Aromatic Aminations – Failure of Pd Chemistry

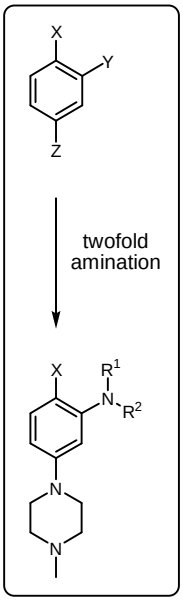
Among transformations which had to be classified as failures was the amination of electron-rich 2-bromoanisole with 3,5-dimethylpyrazole (Table S1, entry 1). *N*-Arylation of this pyrazole already proved to be sluggish for nitroarenes (Table 3, entry 14, methods D4 and E2), but could not be accomplished at all in this case. 2-Bromoanisole did not even give rise to side product formation (e.g. halogen exchange) as observed for the corresponding nitroarenes when using CuI catalysis (method E2).[36] Attempts to alter reactivity within a Pd based procedure by exchange of bases (K_3PO_4 or NaO*t*Pent for Cs_2CO_3, methods D5 and D6)[S1] or ligands (ligand **3a** instead of P*t*Bu$_3$-HBF$_4$, methods C2 and C4) did likewise fail. Obviously an electron rich aryl bromide with sterical hindrance in the *ortho* position in combination with a sterically encumbered pyrazole represents a most unfavorable combination for such an amination reaction.[S2]

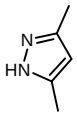
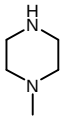
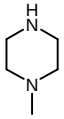
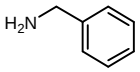
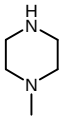
Likewise unsuccessful were the attempts to introduce *N*-methylpiperazine to an *O*-acetylphenol (Table S1, entry 2). Application of the mild BINAP variant using Cs_2CO_3, which is known for displaying a broad functional group compatibility,[13] did not yield any product, so that more aggressive conditions were chosen including the strong base NaO*t*Pent (methods B1 and A), despite the presence of the labile acetyl unit – yielding similar results though.

Halogenated *N*-acetylanilines were known to be problematic substrates for amination reactions, which were only accomplished using the special, highly sterically encumbered ligand **3c** (Figure 1).[6] An attempted coupling of such a substrate with *N*-methylpiperazine (Table S1, entry 3), performed with our standard ligand **3a** as substitute, resulted in only a poor yield (15%, method C4). Same protocol failed to convert a 4-bromoarylsulfonamide (Table S1, entry 4), either with NaO*t*Pent in toluene (method C4) or in *t*BuOH (method C5[6]). In both cases only traces of product were detectable by LCMS.

A second amination step on *N*-acetyl 4-(*N*-methylpiperazinyl)-aniline (Table S1, entry 3) using again method C4 but now for an attempted exchange of 2-chlorine by benzylamine could not be achieved.

Table S1. Unsuccessful amination reactions of 2,4-dihalogenated arenes.



entry	X	Y	Z	1st amination (at Br-site) amine	procedure[a]	yield	2nd amination (at Cl-site) amine	procedure[a]	yield
1	OMe	Br	Cl		C2/C4	-- [b] / traces [c]			
					D4/D5/D6	-- [b]			
					E2	traces [c]			
2	OAc	Cl	Br		A	-- [d]			
					B1/B2	-- [d] / -- [b]			
3	NHAc	Cl	Br		C4 [e]	15% [b]		C4 [f]	-- [b]
4	SO_2NH_2	Cl	Br		C4 [e]/C5	traces [c]			

[a] **A**: Ar-Br / amine 1.0:1.1; 0.05 eq. (DPPF)$PdCl_2$, 0.15 eq. DPPF (**1**), 1.25 eq. NaO*t*Pent, THF (2 mL/mmol), 100°C, 3 h; **B1**: Ar-Br / amine 1.0:1.1; 0.02 eq. Pd_2dba_3, 0.06 eq. BINAP (**2**), 1.4 eq. NaO*t*Pent, toluene (2 mL/mmol Ar-Br), 80°C, 20 h; **B2**: Ar-Br / amine 1.0:1.1; 0.03 eq. $Pd(OAc)_2$, 0.045 eq. BINAP (**2**), 1.4 eq. Cs_2CO_3, toluene (2 mL/mmol Ar-Br), 100°C, 6 h; **C2**: Ar-Br / amine 1.0:1.2; 0.10 eq. $Pd(OAc)_2$, 0.20 eq. (biph)P*t*Bu_2 **3a**, 1.4 eq. K_3PO_4, DME (2 mL/mmol Ar-Br), 100°C, 20 h; **C4**: Ar-Hal / amine 1.0:1.2; 0.05 eq. Pd_2dba_3, 0.20 eq. (biph)P*t*Bu_2 **3a**, 1.4 eq. NaO*t*Pent, toluene (2 mL/mmol Ar-Hal), 110°C, 20 h; **C5**: Ar-Br / amine 1.0:1.1; 0.02 eq. Pd_2dba_3, 0.10 eq. (biph)P*t*Bu_2 **3a**, 2.0 eq. NaO*t*Pent, *t*BuOH (2 mL/mmol Ar-Br), 100°C, 5 h; **D4**: Ar-Br / amine 1.0:1.2; 0.04 eq. Pd_2dba_3, 0.08 eq. P*t*Bu_3-HBF_4, 1.4 eq. Cs_2CO_3, toluene (3 mL/mmol Ar-Br), 100°C, 20 h; **D5**: Ar-Br / amine 1.0:1.2; 0.04 eq. Pd_2dba_3, 0.08 eq. P*t*Bu_3-HBF_4, 1.4 eq. K_3PO_4, toluene (3 mL/mmol Ar-Br), 100°C, 20 h; **D6**: Ar-Br / amine 1.0:1.2; 0.04 eq. Pd_2dba_3, 0.08 eq. P*t*Bu_3-HBF_4, 1.25 eq. NaO*t*Pent, toluene (3 mL/mmol Ar-Br), 100°C, 20 h; **E2**: Ar-Br / amine 1.0:1.2; 0.10 eq. CuI, 0.30 eq. *rac*-**5**, 2.1 eq. K_3PO_4, toluene (1 mL/mmol Ar-Br), 110°C, 20 h; [b] starting haloarene detected / recovered; [c] product traces detected by LCMS, only starting arene detected / recovered; [d] decomposition, some *O*-deacetylated starting material detected (LCMS); [e] Ar-Br / amine 1.0:1.1; 0.02 eq. Pd_2dba_3, 0.10 eq. (biph)P*t*Bu_2 **3a**, 2.0 eq. NaO*t*Pent, 100°C, 5 h; [f] Ar-Cl / amine 1.0:1.3; 0.05 eq. Pd_2dba_3, 0.25 eq. (biph)P*t*Bu_2 **3a**, 2.0 eq. NaO*t*Pent; isolated yields, yields are not optimized.

Comparison of S_NAr and Transition Metal Catalyzed Aromatic Amination

Comparing the scope of transition metal catalyzed aromatic amination and S_NAr protocols, the value of each approach depends highly on the desired substrate combinations:

- For 2,4-dihalogenated nitroarenes, a synthetic chemist seems to be best advised to use a combination of both strategies as they can display complementary advantages depending on the amine to be introduced. With 2,4-difluoro- or -dichloronitroarenes, a consecutive introduction of two different amines is usually achievable by uncatalyzed nucleophilic reactions with good to excellent regioselectivity, with the first amination taking place in the 2-position at ambient temperature and the second one in the 4-position in the presence of base and extensive heating. Only in a few cases the formation of a second regioisomer within the first amination step has been reported as a minor side product (below 10% yield).[S3,S4]
Whereas 5-membered *N*-heteroaromatics (indoles,[43,S5] pyrroles,[43] imidazoles[43,S4,S6] and others[43]) are readily introduced into the 2- or 4-position of correspondingly halogenated nitroarenes by S_NAr methods – not encountering side reactions like Heck-type C-C bond formation – only poor to moderate yields were achieved in our studies using Pd or Cu chemistry (cf. Table 3, entries 13 and 14). Furthermore, a 2-bromo-4-chloro-1-nitrobenzene has to be synthesized first from the corresponding aniline as compared to 2,4-difluoronitrobenzene being commercially available. With regard to alicyclic amines, primary or secondary alkylamines, both approaches qualify for decent product formation with the advantage of generally higher yields and simpler procedures within S_NAr protocols.[43,S4,S7] Benzylamines[43] and anilines[S8] have only rarely been introduced by S_NAr methodology, Pd catalyzed reactions offer an excellent alternative here. As to weak *N*-nucleophiles like amides and carbamates, Pd based chemistry represents the only option resulting in good to excellent yields with Xantphos as ligand (cf. Table 1, entry 2 and Table 3, entries 11, 12, 15-17).

- Changing the substitution pattern in nitroarenes to 2,5-dihalogenated ones, S_NAr protocols can usually only account for amination in the 2-position, even though a nucleophilic replacement of halogen in *meta* position to the head group might be realized under certain conditions ($KF\text{-}Al_2O_3$, 18-crown-6, DMSO, 120°C).[S5] With 1-bromo-4-chloro-2-nitrobenzene and 4-bromo/chloro-1-fluoro-2-nitrobenzene being commercially available, a first amination can easily be performed by either strategy when choosing the starting material appropriately, followed by Pd catalyzed amination in the 5-position.

- Utilizing different head groups, S_NAr aminations become less favorable as they do require strongly electron-withdrawing units with nitro being the by far most activating one. Some successful transformations have been reported with arylsulfones, -ketones and -nitriles[S5,S9] but these do not belong to the repertoire of S_NAr standard transformations. Electron neutral or rich aromatics have successfully been activated for nucleophilic halogen replacement by $?^6$-p-complexation with isolobal $Cr(CO)_3$ and $FeCp^+$ moieties,[S10] but the scope presented thus far is limited and procedures become more complex. For the amination of halogenated heterocycles, especially pyridines, pyrimidines and quinazolines, nucleophilic amines are

usually introduced easily by S_NAr reactions if the halogen is positioned in *ortho* or *para* to the heteroatom. Palladium catalyzed reactions, however, are well elaborated as well.[14,29,40,S11,S12] Using weakly nucleophilic amines or *meta*-halogenated pyridines and 5-bromopyrimidines in such conversions, Pd[14,19,29,40,42,S11] or Cu[25] chemistry would be the method of choice.
Consequently, when abandoning nitro as head group and aiming at a free choice of amination positions relative to the head group, transition metal catalyzed amination reactions represent the only feasible choice with only a few structural limitations. As with S_NAr amination reactions,[43] Pd catalyzed ones can also be performed as parallel syntheses using standard reactor blocks which enable a reaction performance in an inert atmosphere.

Experimental Section

General Remarks

Purifications by preparative TLC were performed on Merck PLC plates, silica gel 60 F_{254}, 1.0 mm or 2.0 mm; for flash chromatography, a Flash Master Personal (Jones Chromatography, UK) and 20 or 50 g silica gel cartridges (Chromabond) were used. ^{1}H NMR spectra were recorded at r.t. on a Bruker Avance 300 MHz, the residual solvent peaks were used as the internal standards (d_6-DMSO: δ 2.49; $CDCl_3$: δ 7.26; CD_3OD: δ 3.35; d_6-acetone: δ 2.05), shifts (d) are given in ppm, coupling constants (*J*) in Hz. Analytical LC/ESI-MS: Waters 600 Multisolvent Delivery System, Waters 600 Controller. Column, Onyx Monolithic C18 (Phenomenex), 50 x 4.6 mm, with stainless steel 2 µm prefilter. Eluent A, H_2O containing 0.1% (v/v) HCO_2H; eluent B, MeCN; gradient, 2% B to 100% B within 4 min (flow, 3 mL/min), then isocratic for 0.90 min (flow, 4 mL/min), then back to 2% B within 0.15 min (flow, 4 mL/min), then isocratic for 0.50 min (flow, 4 mL/min). Mass detection was performed with a Micromass LCZ single quadrupol mass spectrometer with electrospray source using positive and negative ion mode scanning. For UV detection, a Waters 2487 Dual ? Absorbance Detector was set to 254 nm. A Waters Masslynx V 4.0. software was used. Preparative HPLC-MS: Waters 600 Multisolvent Delivery System with peparative pump heads, Waters 600 Controller. At-column dilution: Waters 600 Multisolvent Delivery System with analytical pump heads; Waters 600 Controller; solvent, MeCN-MeOH 80:20 (v/v); flow rate, 0.20 or 1 mL/min. Column, Waters X-Terra RP18, 7 µm, 19 x 150 mm with X-Terra RP18 guard cartridge 7 µm, 19 x 10 mm, used at flow rate 20 mL/min. Eluent A, H_2O containing 0.1% (v/v) HCO_2H; eluent B, MeCN; different linear gradients were individually adapted to sample. Mass detection was performed with a Waters ZQ single quadrupol mass spectrometer with electrospray source using positive or negative ion mode scanning. A Waters Fraction Collector II with mass-triggered fraction collection and, for UV detection, a Waters 2487 Dual ? Absorbance Detector (set to 254 nm) were used, as well as a Waters Masslynx V 4.0 Software.

The following starting materials were synthesized (briefly described in ref.[12]):
- from their corresponding benzoic acids:
methyl 5-bromo-2-chlorobenzoate (Table 1, entry 3): d ($CDCl_3$) = 3.94 (s, 3H), 7.32 (d, *J* = 8.5, 1H), 7.53 (dd, *J* = 8.5/2.4, 1H), 7.97 (d, *J* = 2.4, 1H);
methyl 4-bromo-2-chlorobenzoate (Table 4, entries 18-20): d ($CDCl_3$) = 3.91 (s, 3H), 7.44 (dd, *J* = 8.4/1.9, 1H), 7.62 (d, *J* = 1.9, 1H), 7.70 (d, *J* = 8.4, 1H);
- from their corresponding anilines:
4-bromo-2-chloro-1-nitrobenzene (Table 2): d ($CDCl_3$) = 7.56 (dd, *J* = 8.6/2.0, 1H), 7.74 (d, *J* = 2.0, 1H), 7.79 (d, *J* = 8.6, 1H);
2-bromo-4-chloro-1-nitrobenzene (Table 3): d ($CDCl_3$) = 7.44 (dd, *J* = 8.7/2.2, 1H), 7.77 (d, *J* = 2.2, 1H), 7.84 (d, *J* = 8.7, 1H);

- from their corresponding phenols:
4-bromo-2-chloroanisole (Table 5, entries 24-26): d ($CDCl_3$) = 3.88 (s, 3H), 6.79 (d, *J* = 8.8, 1H), 7.33 (dd, *J* = 8.8/2.4, 1H), 7.50 (d, *J* = 2.4, 1H);
1-(benzyloxy)-4-bromo-2-chlorobenzene (Table 5, entries 24-26): d ($CDCl_3$) = 5.14 (s, 2H), 6.83 (d, *J* = 8.8, 1H), 7.28 (dd, *J* = 8.8/2.4, 1H), 7.32 (t, *J* = 6.8, 1H), 7.39 (dd, *J* = 7.4/6.8, 2H), 7.44 (d, *J* = 7.4, 2H), 7.52 (d, *J* = 2.4, 1H);
1-(benzyloxy)-2-bromo-4-chlorobenzene (only mentioned in the text, not shown): d ($CDCl_3$) = 5.14 (s, 2H), 6.85 (d, *J* = 8.8, 1H), 7.20 (dd, *J* = 8.8/2.5, 1H), 7.34 (t, *J* = 6.9, 1H), 7.40 (dd, *J* = 7.4/6.9, 2H), 7.46 (d, *J* = 7.4, 2H), 7.57 (d, *J* = 2.5, 1H).

4-bromo-2-chlorophenyl acetate (Table S1, entry 2): NaH (312 mg, 13 mmol) was suspended in THF (25 mL) and 4-bromo-2-chlorophenol (2.08 g, 10 mmol) was added in small portions at 0°C. Upon stirring for 30 min at this temp. and additional 30 min at r.t., acetyl chloride (942 mg, 856 µL, 12 mmol) was added again at 0°C, and the mixture stirred at r.t. for 5 h. The reaction was quenched by careful addition of H_2O, and was partitioned between Et_2O and half-sat. aq. $NaHCO_3$. Flash chromatography on silica gel (pure PE to PE/EtOAc 20:1) yielded pure product as a yellow oil (1.76 g, 7.1 mmol, 71%): d ($CDCl_3$) = 2.34 (s, 3H), 7.01 (d, *J* = 8.6, 1H), 7.39 (dd, *J* = 8.6/2.3, 1H), 7.60 (d, *J* = 2.3, 1H).

***N*-(4-bromo-2-chlorophenyl)acetamide** (Table S1, entry 3): 4-bromo-2-chloroaniline (2.06 g, 10 mmol) was dissolved in CH_2Cl_2 (20 mL) and acetic anhydride (2.04 g, 1.89 mL, 20 mmol) was added at r.t. Upon stirring overnight, workup followed the procedure described above for 4-bromo-2-chlorophenyl acetate to yield pure product as a colorless powder (1.46 g, 5.9 mmol, 59%): d ($CDCl_3$) = 2.23 (s, 3H), 7.39 (dd, *J* = 8.8/2.2, 1H), 7.52 (d, *J* = 2.2, 1H), 7.54 (br, NH), 8.29 (d, *J* = 8.8, 1H).

***tert*-butyl benzylcarbamate (a) and *tert*-butyl furan-2-ylmethylcarbamate (b)**: The respective amine was dissolved in THF, 1.5 eq. Boc_2O were added, and the mixture was stirred at r.t. overnight. The solvent was removed, sat. aq. $NaHCO_3$ was added, and the aq. phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and the solvent was removed. Impurities were stripped off by lyophilization of the product.
(a) d ($CDCl_3$) = 1.47 (s, 9H), 4.31 (d, *J* = 5.8, 2H), 4.85 (br, NH), 7.22-7.36 (m, 5H);
(b) d ($CDCl_3$) = 1.45 (s, 9H), 4.29 (d, *J* = 5.6, 2H), 4.81 (br, NH), 6.20 (d, *J* = 3.0, 1H), 6.31 (dd, *J* = 3.0/1.8, 1H), 7.34 (dd, *J* = 1.8/0.8, 1H).

Workup of amination reactions, Tables 1-5, S1 and Scheme 1:
A) The reaction mixture was taken up in half-sat. brine and extracted with EtOAc. Combined organic phases were re-extracted with 5% aq. HCl. The acidic aq. phase was concd and product isolation was achieved using prep. HPLC (RP18). The resulting product was taken up in $CHCl_3$ and extracted with sat. aq. $NaHCO_3$, and the organic phase was dried over $MgSO_4$;
B) The reaction mixture was taken up in half-sat. brine and extracted with EtOAc. Combined organic phases were dried over $MgSO_4$, concd and purified by prep. HPLC (RP18). The resulting product was taken up in $CHCl_3$, extracted with sat. aq. $NaHCO_3$, and the organic phase was dried over $MgSO_4$;
C) The mixture was filtered through a pipette stuffed with cotton wool and then directly mounted on a prep. TLC plate (for reactions with up to 1.2 mmol aryl halide: 1 mm silica gel plate per 0.4 mmol starting aryl halide), reaction solvent was dried away in a vigorous stream of air, and separation was achieved using PE/EtOAc (v:v) or PE/CH_2Cl_2/MeOH (v:v:v) mixtures. For reactions started with over 1.2 mmol aryl halide, the mixture was directly mounted on silica gel and separated using Flash Master Personal (20 or 50 g silica gel cartridge, gradient from 100% PE to 50:50 PE/EtOAc);
D) The reaction mixture was taken up in half-sat. brine and extracted with EtOAc. Combined organic phases were dried over $MgSO_4$, concd and purified by prep. TLC. Separation was achieved using PE/EtOAc (v:v) mixtures;
E) The reaction mixture was concd, the residue was taken up in H_2O and MeOH (total volume < 10 mL) and purification was achieved by prep. HPLC (RP18). The resulting product was taken up in $CHCl_3$, extracted with sat. aq. $NaHCO_3$, and the organic phase was dried over $MgSO_4$;
F) Final purification of HPLC fractions by prep. TLC was performed – if necessary – with either PE/CH_2Cl_2/MeOH (v:v:v) or CH_2Cl_2/MeOH (v:v) mixtures.

Workup, MS and NMR data for compounds of Table 1; all NMR spectra were determined in $CDCl_3$.

entry	workup	LCMS $[M+1]^+$	^{1}H-NMR shifts, central Ar	^{1}H-NMR shifts, 2-amino group	^{1}H-NMR shifts, 5-amino group
1	A	-- [a]	6.78 (d, *J* = 9.2, 1H), ~7.39 (1H in m of 2-amino group), 8.19 (d, *J* = 2.5, 1H)	4.54 (d, *J* = 5.7, 2H), 8.39 (br, NH), 7.30-7.41 (m, 5H)	--
2	C (7:1)	-- [a]	6.89 (br, 1H), 7.36 (d, *J* = 7.8, 1H), 7.88 (br, 1H)	1.33 (s, 9H), 4.36, 5.23 (each d, *J* = 14.8, 1H), 7.24-7.35 (m, 5H)	--
	E	427	6.77-6.90 (m, 2H), ~7.32 (1H in m of 2-amino group)	1.33 (s, 9H), 4.26, 5.24 (each d, *J* = 14.7, 1H), 7.20-7.41 (m, 5H)	2.33 (s, 3H), 2.53 (t, *J* = 5.0, 4H), 3.22 (t, *J* = 5.0, 4H)
3	A	269/271	3.83 (s, 3H), 6.84 (dd, *J* = 8.8/3.0, 1H), 7.18 (d, *J* = 8.8, 1H), 7.23 (d, *J* = 3.0, 1H)	--	2.25 (s, 3H), 2.46 (t, *J* = 5.1, 4H), 3.12 (t, *J* = 5.1, 4H)
	E+F (6:4:1)	340	3.86 (s, 3H), 6.61 (d, *J* = 9.1, 1H), 7.05 (dd, *J* = 9.1/3.0, 1H), 7.53 (d, *J* = 3.0, 1H)	4.43 (d, *J* = 5.5, 2H), 7.21-7.38 (m, 5H), 7.85 (br t, *J* = 5.5, NH)	2.41 (s, 3H), 2.67 (t, *J* = 4.8, 4H), 3.10 (t, *J* = 4.8, 4H)
4	A	241/243	3.87 (s, 3H), 6.43 (dd, *J* = 8.7/2.7, 1H), 6.49 (d, *J* = 2.7, 1H), 7.18 (d, *J* = 8.7, 1H)	--	2.34 (s, 3H), 2.56 (t, *J* = 5.1, 4H), 3.18 (t, *J* = 5.1, 4H)
	E+F (6:4:1)	312	3.82 (s, 3H), 6.43 (dd, *J* = 8.6/2.4, 1H), 6.52 (d, *J* = 8.6, 1H), 6.54 (d, *J* = 2.4, 1H)	4.06 (br, NH), 4.29 (s, 2H), 7.24 (tt, *J* = 7.0/1.7, 1H), 7.31 (t, *J* = 7.0, 2H), 7.37 (d, *J* = 7.0, 2H)	2.34 (s, 3H), 2.58 (t, *J* = 4.9, 4H), 3.07 (t, *J* = 4.9, 4H)

[a] product can not be ionized under LCMS conditions.

Workup, MS and NMR data for compounds of Table 2; NMR spectra were determined in $CDCl_3$ if not stated otherwise.

entry	workup	LCMS $[M+1]^+$	central Ar	2-amino group	4-amino group
5-8	A	256/258	6.70 (dd, *J* = 9.4/2.8, 1H), 6.82 (d, *J* = 2.8, 1H), 7.98 (d, *J* = 9.4, 1H)	--	2.33 (s, 3H), 2.52 (t, *J* = 5.1, 4H), 3.38 (t, *J* = 5.1, 4H)
5	E	345	5.82 (d, *J* = 2.4, 1H), 6.23 (dd, *J* = 9.7/2.4, 1H), 8.09 (d, *J* = 9.7, 1H)	4.47 (d, *J* = 5.4, 2H), 7.05 (t, *J* = 8.5, 2H), 7.33 (dd, *J* = 8.5/3.0, 2H), 8.73 (br, NH)	2.41 (s, 3H), 2.60 (br, 4H), 3.37 (t, *J* = 4.9, 4H)
6 [a]	E	302	5.37 (d, *J* = 2.7, 1H), 6.46 (dd, *J* = 9.6/2.7, 1H), 8.10 (d, *J* = 9.6, 1H)	6.25 (t, *J* = 2.3, 2H), 6.77 (t, *J* = 2.3, 2H), 8.17 (s, NH)	2.76 (s, 3H), 3.10 (t, *J* = 5.1, 4H), 3.47 (t, *J* = 5.1, 4H)
7	E	330	5.69 (d, *J* = 2.6, 1H), 6.23 (dd, *J* = 9.7/2.6, 1H), 8.06 (d, *J* = 9.7, 1H)	3.62 (q, *J* = 6.1, 2H), 4.20 (t, *J* = 6.1, 2H), 6.17 (t, *J* = 2.1, 2H), 6.71 (t, *J* = 2.1, 2H), 8.49 (br t, *J* = 5.1, NH)	2.37 (s, 3H), 2.54 (t, 4H), 3.39 (t, 4H)
8	E+F (9:1)	357	6.01 (d, *J* = 2.6, 1H), 6.25 (dd, *J* = 9.7/2.6, 1H), 8.08 (d, *J* = 9.7, 1H)	3.70 (q, *J* = 5.6, 2H), 4.26 (t, *J* = 5.6, 2H), 6.94 (d, *J* = 8.7, 2H), 6.98 (t, *J* = 7.4, 1H), 7.30 (dd, *J* = 8.7/7.4, 2H), 8.66 (br, NH)	2.37 (s, 3H), 2.55 (t, *J* = 5.0, 4H), 3.43 (t, *J* = 5.0, 4H)
9	A	298/300	6.69 (dd, *J* = 9.4/2.9, 1H), 6.81 (d, *J* = 2.9, 1H), 7.97 (d, *J* = 9.4, 1H)	--	0.91 (t, *J* = 7.2, 3H), 1.33 (sext, *J* = 7.2, 2H), 1.48 (m, 2H), 2.37 (t, *J* = 7.5, 2H), 2.54 (t, *J* = 5.2, 4H), 3.37 (t, *J* = 5.2, 4H)
[b]	E+F (16:4:1)	369	6.08 (d, *J* = 2.6, 1H), 6.39 (dd, *J* = 9.7/2.6, 1H), 7.98 (d, *J* = 9.7, 1H)	4.64 (d, *J* = 5.7, 2H), 7.29 (t, *J* = 7.2, 1H), 7.38 (t, *J* = 7.2, 2H), 7.46 (d, *J* = 7.2, 2H), 8.78 (br, NH)	0.91 (t, *J* = 7.2, 3H), 1.34 (sext, *J* = 7.2, 2H), 1.47 (quin, *J* = 7.2, 2H), 2.32 (t, *J* = 7.2, 2H), 2.46 (t, *J* = 5.1, 4H), 3.36 (t, *J* = 5.1, 4H)
10	A	319/321	6.74 (dd, *J* = 9.4/2.8, 1H), 6.86 (d, *J* = 2.8, 1H), 8.03 (d, *J* = 9.4, 1H)	--	3.53-3.57 (m, 4H), 3.73-3.76 (m, 4H), 6.66 (d, *J* = 8.5, 1H), 6.68 (ddd, *J* = 7.2/4.9/0.9, 1H), 7.53 (ddd, *J* = 8.5/7.2/1.9, 1H), 8.21 (ddd, *J* = 4.9/1.9/0.9, 1H)
	E+F (9:1)	390	5.86 (d, *J* = 2.6, 1H), 6.46 (dd, *J* = 9.7/2.6, 1H), 8.12 (d, *J* = 9.7, 1H)	4.53 (d, *J* = 5.6, 2H), 7.21-7.39 (m, 5H), 8.22 (br, NH)	3.46 (br, 2H), 3.63-3.77 (m, 6H), 6.24 (dd, *J* = 7.5/2.5, 1H), 6.69 (m, 1H), 7.52 (m, 1H), 8.21 (m, 1H)

[a] $CDCl_3/CD_3OD$ mixture; [b] d_6-acetone.

Workup, MS and NMR data for compounds of Table 3; NMR spectra were determined in $CDCl_3$ if not stated otherwise.

entry	workup	LCMS $[M+1]^+$	central Ar	2-amino group	4-amino group
11	C (FM)	-- [b]	7.02 (br, 1H), 7.27-7.38 (m, 6H), 7.87 (d, *J* = 8.7, 1H)	1.36 (s, 9H), 4.49, 5.21 (each d, *J* = 13.7, 1H), 7.24-7.35 (m, 5H)	--
[c]	E+F (9:1)	427	6.10/6.27 (d, *J* = 2.3, 1H), 6.63/6.66 (dd, *J* = 9.3/2.3, 1H), 7.97/8.06 (d, *J* = 9.3, 1H)	1.34/1.52 (s, 9H), 4.18/4.12, 5.42/5.26 (each d, *J* = 14.9, 1H), 7.24-7.35 (m, 5H)	2.31 (s, 3H), 2.43 (t, *J* = 4.8, 4H), 3.04-3.19 (m, 4H)
12	C (FM)	-- [b]	7.17 (br, 1H), 7.35 (dd, *J* = 8.8/2.2, 1H), 7.88 (d, *J* = 8.8, 1H)	1.31/1.54 (s, 9H) [c], 4.47, 5.13 (each d, *J* = 15.6, 1H), 6.26, 6.32, 7.38 (each br, 1H)	--
[c]	E+F (9:1)	417	6.36/6.52 (d, *J* = 2.7, 1H), 6.67/6.71 (dd, *J* = 9.3/2.7, 1H), 7.98/8.06 (d, *J* = 9.3, 1H)	1.31/1.52 (s, 9H), 4.29/4.27, 5.27/5.10 (each d, *J* = 15.4, 1H), 6.23/6.18 (d, *J* = 2.9, 1H), 6.29 (dd, *J* = 2.9/1.9, 1H), 7.35 (dd, *J* = 1.9/0.8, 1H)	2.34 (s, 3H), 2.50 (t, *J* = 5.1, 4H), 3.25-3.35 (m, 4H)
13	E+F (5:1) [d]	-- [b]	7.37 (dd, *J* = 8.7/2.2, 1H), 7.43 (d, *J* = 2.2, 1H), 7.78 (d, *J* = 8.7, 1H)	2.13 (s, 3H), 6.20 (dd, *J* = 2.6/1.8, 1H), 6.54 (m, 1H), 6.67 (t, *J* = 2.6, 1H)	--
	E	301	6.67 (d, *J* = 2.8, 1H), 6.74 (dd, *J* = 9.3/2.8, 1H), 7.94 (d, *J* = 9.3, 1H)	2.14 (s, 3H), 6.16 (t, *J* = 2.1, 1H), 6.53 (br, 1H), 6.66 (t, *J* = 2.5, 1H)	2.34 (s, 3H), 2.54 (t, *J* = 5.1, 4H), 3.40 (t, *J* = 5.1, 4H)
14	E+F (5:1) [d]	252/254	7.50 (d, *J* = 2.3, 1H), 7.53 (dd, *J* = 8.5/2.3, 1H), 7.95 (d, *J* = 8.5, 1H)	2.18, 2.25 (each s, 3H), 6.02 (s, 1H)	--
	E	316	6.77 (d, *J* = 2.9, 1H), 6.86 (dd, *J* = 9.3/2.9, 1H), 8.09 (d, *J* = 9.3, 1H)	2.10, 2.28 (each s, 3H), 6.00 (s, 1H)	2.35 (s, 3H), 2.54 (t, *J* = 5.1, 4H), 3.44 (t, *J* = 5.1, 4H)
15	C (5:1)	291/293	7.25-7.40 (m, 2H), 7.82 (br, 1H)	3.42 (s, 3H), 7.25-7.40 (m, 5H)	--
	E	355	6.46 (br, 1H), 6.64 (br, 1H), 7.82 (br, 1H)	3.39 (s, 3H), 7.10-7.40 (m, 5H)	2.33 (s, 3H), 2.48 (br, 4H), 3.29 (br, 4H)
16	D (4:1)	277/279 [e]	7.17 (dd, *J* = 9.1/2.3, 1H), 8.23 (d, *J* = 9.1, 1H), 9.13 (d, *J* = 2.3, 1H)	7.54 (ddt, *J* = 7.3/7.0/1.5, 2H), 7.62 (tt, *J* = 7.3/1.5, 1H), 7.98 (dt, *J* = 7.0/1.5, 2H), 11.41 (br, NH)	--
	E	341	6.57 (dd, *J* = 9.7/2.8, 1H), 8.21 (d, *J* = 9.7, 1H), 8.60 (d, *J* = 2.8, 1H)	7.53 (dd, *J* = 7.4/6.8, 2H), 7.60 (tt, *J* = 7.4/1.6, 1H), 8.01 (dt, *J* = 6.8/1.6, 2H), 12.03 (br, NH)	2.38 (s, 3H), 2.58 (t, *J* = 5.1, 4H), 3.58 (t, *J* = 5.1, 4H)
17 [a]	E	252/254	7.72 (dd, *J* = 9.3/2.3, 1H), 7.72 (d, *J* = 2.3, 1H), 8.16 (d, *J* = 9.3, 1H)	7.08 (dd, *J* = 9.6/1.5, 1H), 7.53 (dd, *J* = 9.6/3.9, 1H), 8.08 (dd, *J* = 3.9/1.5, 1H)	--
	E+F (9:1)	316	6.79 (d, *J* = 2.8, 1H), 6.88 (dd, *J* = 9.4/2.8, 1H), 8.16 (d, *J* = 9.4, 1H)	7.03 (dd, *J* = 9.6/1.6, 1H), 7.29 (dd, *J* = 9.6/3.8, 1H), 7.87 (dd, *J* = 3.8/1.6, 1H)	2.35 (s, 3H), 2.54 (t, *J* = 5.1, 4H), 3.45 (t, *J* = 5.1, 4H)

[a] $CDCl_3/CD_3OD$ mixture; [b] product can not be ionized under LCMS conditions; [c] two rotamers, ratio ~2:1, shift of major isomer given first; [d] prep. TLC was performed with a PE/EtOAc (v:v) mixture; [e] product only negatively ionizable, $[M-1]^-$.

Workup, MS and NMR data for compounds of Tables 4, 5 and S1; NMR spectra were determined in $CDCl_3$ if not stated otherwise.

entry	workup	LCMS $[M+1]^+$	central Ar	2-amino group	4-amino group
18-20	B	269/271	3.86 (s, 3H), 6.72 (dd, *J* = 8.9/2.6, 1H), 6.86 (d, *J* = 2.6, 1H), 7.83 (d, *J* = 8.9, 1H)	--	2.33 (s, 3H), 2.52 (t, *J* = 5.1, 4H), 3.32 (t, *J* = 5.1, 4H)
18	E+F (9:1)	340	3.81 (s, 3H), 5.95 (d, *J* = 2.4, 1H), 6.17 (dd, *J* = 9.0/2.4, 1H), 7.78 (d, *J* = 9.0, 1H)	4.43 (d, *J* = 5.5, 2H), 7.24 (t, *J* = 7.0, 1H), 7.32 (dd, *J* = 7.9/7.0, 2H), 7.37 (d, *J* = 7.9, 2H), 8.21 (br t, *J* = 5.1, NH)	2.32 (s, 3H), 2.48 (t, *J* = 5.1, 4H), 3.23 (t, *J* = 5.1, 4H)
19 [a]	E	330	3.82 (s, 3H), 6.20 (d, *J* = 2.3, 1H), 6.30 (dd, *J* = 9.1/2.3, 1H), 7.78 (d, *J* = 9.1, 1H)	4.46 (s, 2H), 6.31 (m, 1H), 6.39 (m, 1H), 7.47 (br, 1H)	2.50 (s, 3H), 2.77 (t, *J* = 4.8, 4H), 3.40 (t, *J* = 4.8, 4H)
20 [a]	E	354	3.77 (s, 3H), 6.07 (d, *J* = 2.4, 1H), 6.22 (dd, *J* = 9.0/2.4, 1H), 7.73 (d, *J* = 9.0, 1H)	2.96 (t, *J* = 7.0, 2H), 3.46 (t, *J* = 7.0, 2H), 7.19-7.35 (m, 5H)	2.34 (s, 3H), 2.56 (t, *J* = 5.1, 4H), 3.32 (t, *J* = 5.1, 4H)
21-23 [a]	A	236/238	6.82 (dd, *J* = 8.9/2.6, 1H), 6.95 (d, *J* = 2.6, 1H), 7.41 (d, *J* = 8.9, 1H)	--	2.24 (s, 3H), 2.46 (t, *J* = 5.2, 4H), 3.30 (t, *J* = 5.2, 4H)
21	E	307	5.98 (d, *J* = 2.3, 1H), 6.23 (dd, *J* = 8.8/2.3, 1H), 7.25 (d, *J* = 8.8, 1H)	4.40 (d, *J* = 5.4, 2H), 4.89 (br t, *J* = 5.2, NH), 7.26-7.36 (m, 5H)	2.31 (s, 3H), 2.47 (t, *J* = 5.1, 4H), 3.22 (t, *J* = 5.1, 4H)
22	E	297	6.08 (d, *J* = 2.2, 1H), 6.22 (dd, *J* = 8.8/2.2, 1H), 7.21 (d, *J* = 8.8, 1H)	4.36 (d, *J* = 5.5, 2H), 4.83 (br t, *J* = 5.5, NH), 6.23 (m, 1H), 6.31 (dd, *J* = 3.2/1.9, 1H), 7.35 (dd, *J* = 1.9/0.7, 1H)	2.31 (s, 3H), 2.49 (t, *J* = 5.1, 4H), 3.26 (t, *J* = 5.1, 4H)
23	E	337	6.10 (d, *J* = 2.3, 1H), 6.25 (dd, *J* = 8.9/2.3, 1H), 7.25 (d, *J* = 8.9, 1H)	3.61 (q, *J* = 5.6, 2H), 4.19 (t, *J* = 5.6, 2H), 4.82 (br t, *J* = 5.6, NH), 6.93 (d, *J* = 8.7, 2H), 6.98 (t, *J* = 7.4, 1H), 7.29 (dd, *J* = 8.7/7.4, 2H)	2.34 (s, 3H), 2.52 (t, *J* = 5.1, 4H), 3.31 (t, *J* = 5.1, 4H)
24-26 [b]	A	241/243	3.84 (s, 3H), 6.79 (dd, *J* = 8.9/2.8, 1H), 6.86 (d, *J* = 2.8, 1H), 6.98 (d, *J* = 8.9, 1H)	--	2.35 (s, 3H), 2.57 (t, *J* = 5.0, 4H), 3.11 (t, *J* = 5.0, 4H)
24 [b]	E+F (95:5)	312	3.80 (s, 3H), 6.23 (dd, *J* = 8.5/2.7, 1H), 6.29 (d, *J* = 2.7, 1H), 6.69 (d, *J* = 8.5, 1H)	4.34 (s, 2H), 7.26 (tt, *J* = 6.9/1.7, 1H), 7.34 (ddd, *J* = 8.1/6.9/1.7, 2H), 7.39 (d, *J* = 8.1, 2H)	2.34 (s, 3H), 2.56 (t, *J* = 5.0, 4H), 3.06 (t, *J* = 5.0, 4H)
25 [b]	E+F (85:15)	302	3.78 (s, 3H), 6.25 (dd, *J* = 8.6/2.7, 1H), 6.37 (d, *J* = 2.7, 1H), 6.68 (d, *J* = 8.6, 1H)	4.32 (s, 2H), 4.55 (br, NH), 6.23 (m, 1H), 6.31 (dd, *J* = 3.2/1.9, 1H), 7.35 (dd, *J* = 1.9/0.8, 1H)	2.35 (s, 3H), 2.58 (t, *J* = 5.0, 4H), 3.10 (t, *J* = 5.0, 4H)
26 [b]	E+F (9:1)	326	3.77 (s, 3H), 6.24 (dd, *J* = 8.6/2.7, 1H), 6.34 (d, *J* = 2.7, 1H), 6.68 (d, *J* = 8.6, 1H)	2.96 (t, *J* = 7.3, 2H), 3.41 (t, *J* = 7.3, 2H), 4.00 (br, NH), 7.20-7.36 (m, 5H)	2.37 (s, 3H), 2.60 (t, *J* = 5.0, 4H), 3.13 (t, *J* = 5.0, 4H)
24-26 [a,c]	A	317/319	5.11 (s, 2H), 6.88 (dd, *J* = 9.0/2.9, 1H), 7.04 (d, *J* = 9.0, 1H), 7.06 (d, *J* = 2.9, 1H), 7.33 (tt, *J* = 7.2/1.6, 1H), 7.40 (tt, *J* = 7.2/1.8, 2H), 7.48 (d, *J* = 7.2, 2H)	--	2.37 (s, 3H), 2.63 (t, *J* = 5.1, 4H), 3.14 (t, *J* = 5.1, 4H)
24 [c]	E	388	5.03 (s, 2H), 6.20 (dd, *J* = 8.6/2.7, 1H), 6.27 (d, *J* = 2.7, 1H), 6.76 (d, *J* = 8.6, 1H), 7.20-7.44 (m, 5H)	4.35 (s, 2H), 4.69 (br, NH), 7.20-7.44 (m, 5H)	2.32 (s, 3H), 2.53 (t, *J* = 5.0, 4H), 3.04 (t, *J* = 5.0, 4H)
25 [c]	E	378	5.02 (s, 2H), 6.23 (dd, *J* = 8.6/2.7, 1H), 6.38 (d, *J* = 2.7, 1H), 6.75 (d, *J* = 8.6, 1H), 7.28-7.44 (m, 5H)	4.33 (s, 2H), 4.65 (br, NH), 6.21 (m, 1H), 6.30 (dd, *J* = 3.2/1.9, 1H), 7.28-7.44 (m, 1H)	2.35 (s, 3H), 2.58 (t, *J* = 5.0, 4H), 3.10 (t, *J* = 5.0, 4H)
26 [c]	E	402	4.95 (s, 2H), 6.20 (dd, *J* = 8.6/2.7, 1H), 6.33 (d, *J* = 2.7, 1H), 6.74 (d, *J* = 8.6, 1H), 7.18-7.40 (m, 5H)	2.92 (t, *J* = 7.0, 2H), 3.39 (t, *J* = 7.0, 2H), 4.32 (br, NH), 7.18-7.40 (m, 5H)	2.35 (s, 3H), 2.58 (t, *J* = 5.0, 4H), 3.12 (t, *J* = 5.0, 4H)
S1, 3 [a]	E	268/270	2.18 (s, 3H), 6.94 (dd, *J* = 8.9/2.8, 1H), 7.05 (d, *J* = 2.8, 1H), 7.48 (d, *J* = 8.9, 1H)	--	2.38 (s, 3H), 2.63 (t, *J* = 5.1, 4H), 3.24 (t, *J* = 5.1, 4H)

[a] CD_3OD; [b] X = OMe; [c] X = OBn.

side products (Tables 1-5, Figure 2):
***N*^{1},*N*^{4}-dibenzyl-*N*^{4}-(4-chloro-2-nitrophenyl)-2-nitrobenzene-1,4-diamine (6)**, LCMS $[M+2]^{++}$ = 245/247, $[M-1]^-$ = 487/489;
4,4'-dichloro-2,2'-dinitrobiphenyl (7a), LCMS: product can not be ionized; d ($CDCl_3$) = 7.24 (d, *J* = 8.2, 2H), 7.68 (dd, *J* = 8.2/2.1, 2H), 8.23 (d, *J* = 2.1, 2H);
5,5'-dichloro-2,2'-dinitrobiphenyl (7b), LCMS: product can not be ionized; d ($CDCl_3$) = 7.31 (d, *J* = 2.3, 2H), 7.59 (dd, *J* = 8.7/2.3, 2H), 8.23 (d, *J* = 8.7, 2H);
1-methyl-4-(4-nitro-3-phenoxyphenyl)piperazine (9), LCMS $[M+1]^+$ = 314; d ($CDCl_3$) = 2.32 (s, 3H), 2.49 (t, *J* = 5.1, 4H), 3.30 (t, *J* = 5.1, 4H), 6.35 (d, *J* = 2.7, 1H), 6.60 (dd, *J* = 9.4/2.7, 1H), 7.01 (d, *J* = 8.5, 2H), 7.12 (t, *J* = 7.4, 1H), 7.35 (dd, *J* = 8.5/7.4, 2H), 8.07 (d, *J* = 9.4, 1H);
4-chloro-2-nitro-1-phenoxybenzene (entry 2), LCMS: product can not be ionized; d ($CDCl_3$) = 6.96 (d, *J* = 9.0, 1H), 7.04 (d, *J* = 8.7, 2H), 7.20 (tt, *J* = 7.4/1.1, 1H) 7.39 (dd, *J* = 8.7/7.4, 2H), 7.35 (dd, *J* = 9.0/2.6, 1H), 7.93 (d, *J* = 2.6, 1H);
2-(2-(5-(4-methylpiperazin-1-yl)-2-nitrophenyl)-1H-pyrrol-1-yl)ethanamine (entry 7), LCMS $[M+1]^+$ = 330; d (CD_3OD) = 2.55 (s, 3H), 2.86 (t, *J* = 5.1, 4H), 3.08 (t, *J* = 6.7, 2H), 3.56 (t, *J* = 5.1, 4H), 4.07 (t, *J* = 6.7, 2H), 6.06 (dd, *J* = 3.5/1.7, 1H), 6.25 (dd, *J* = 3.5/2.8, 1H), 6.83 (d, *J* = 2.9, 1H), 6.89 (dd, *J* = 2.8/1.7, 1H), 6.99 (dd, *J* = 9.3/2.9, 1H), 8.08 (d, *J* = 9.3, 1H);
2-(5-chloro-2-nitrophenyl)-3-methyl-1*H*-pyrrole (a) and 3-(5-chloro-2-nitrophenyl)-4-methyl-1*H*-pyrrole (b), two different products of Heck-arylation (entry 13): LCMS $[M-1]^-$ = 235/237; (a) d ($CDCl_3$) = 6.15 (t, *J* = 2.7, 1H), 6.83 (t, *J* = 2.7, 1H), 7.38 (dd, *J* = 8.7/2.3, 1H), 7.45 (d, *J* = 2.3, 1H), 7.80 (d, *J* = 8.7, 1H); (b) d ($CDCl_3$) = 6.36 (br, 1H), 6.71 (br, 1H), 7.26 (dd, *J* = 8.6/2.2, 1H), 7.57 (d, *J* = 2.2, 1H), 7.67 (d, *J* = 8.6, 1H);
3,3'-dibromo-4,4'-dinitrobiphenyl (entry 14), LCMS: product can not be ionized; d ($CDCl_3$) = 7.31 (dd, *J* = 8.8/2.3, 2H), 7.57 (d, *J* = 2.3, 2H), 8.37 (d, *J* = 8.8, 2H);
3-(5-chloro-2-nitrophenoxy)pyridazine (entry 17), LCMS: product can not be ionized; d (CD_3OD) = 7.60 (dd, *J* = 8.8/2.3, 1H), 7.61 (dd, *J* = 8.9/1.2, 1H), 7.67 (d, *J* = 2.3, 1H), 7.85 (dd, *J* = 8.9/4.6, 1H), 8.23 (d, *J* = 8.8, 1H), 9.00 (dd, *J* = 4.6/1.2, 1H);
***tert*-pentyl 2-chloro-4-(4-methylpiperazin-1-yl)benzoate** (entry 18, first amination), LCMS $[M+1]^+$ = 325/327;
methyl 4-(4-methylpiperazin-1-yl)-2-(*tert*-pentyloxy)benzoate (entry 18, first amination), LCMS $[M+1]^+$ = 321;
***tert*-pentyl 2-(benzylamino)-4-(4-methylpiperazin-1-yl)benzoate** (entry 18), LCMS $[M+1]^+$ = 396;
***tert*-pentyl 2-(furan-2-ylmethylamino)-4-(4-methylpiperazin-1-yl)benzoate** (entry 19), LCMS $[M+1]^+$ = 386; d (CD_3OD) = 0.98 (t, *J* = 7.5, 3H), 1.56 (s, 6H), 1.93 (q, *J* = 7.5, 2H), 2.72 (s, 3H), 3.06 (br, 4H), 3.48 (br, 4H), 4.45 (s, 2H), 6.23 (d, *J* = 2.5, 1H), 6.29 (dd, *J* = 8.9/2.5, 1H), 6.33 (m, 1H), 6.40 (m, 1H), 7.48 (m, 1H), 7.76 (d, *J* = 8.9, 1H);
bromo-iodo exchange (entries 2, 13-15), LCMS: products can not be ionized;
4-chloro-2-iodonitroarene: d ($CDCl_3$) = 7.47 (dd, *J* = 8.7/2.2, 1H), 7.84 (d, *J* = 8.7, 1H), 8.06 (d, *J* = 2.2, 1H);
5-chloro-2-iodonitroarene: d ($CDCl_3$) = 7.26 (dd, *J* = 8.5/2.4, 1H), 7.85 (d, *J* = 2.4, 1H), 7.96 (d, *J* = 8.5, 1H).

products Scheme 1: workup C (3:9:1), products crystallized from $CHCl_3/Et_2O$;
***N*-(4-(benzo[*d*]thiazol-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)pyrimidin-2-amine (12)**, LCMS $[M+1]^+$ = 403; d (d_6-DMSO) = 2.23 (s, 3H), 2.39 (t, *J* = 5.0, 4H), 3.63 (t, *J* = 5.0, 4H), 6.34 (d, *J* = 6.1, 1H), 7.40 (ddd, *J* = 8.1/7.1/1.2, 1H), 7.51 (ddd, *J* = 8.4/7.1/1.2, 1H), 7.93 (d, *J* = 8.9, 2H), 7.99 (d, *J* = 8.9, 2H), 7.99 (d, *J* = 8.1, 1H), 8.03 (d, *J* = 6.1, 1H), 8.09 (d, *J* = 8.4, 1H), 9.47 (s, NH);

***N*-(3-(benzo[*d*]thiazol-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)pyrimidin-2-amine (14)**, LCMS $[M+1]^+$ = 403; d (d_6-DMSO) = 2.24 (s, 3H), 2.42 (t, *J* = 4.8, 4H), 3.68 (t, *J* = 4.8, 4H), 6.32 (d, *J* = 6.1, 1H), 7.42 (t, *J* = 8.0, 1H), 7.47 (ddd, *J* = 7.9/7.0/1.2, 1H), 7.56 (ddd, *J* = 8.4/7.0/1.2, 1H), 7.62 (d, *J* = 8.0, 1H) 7.72 (dd, *J* = 8.0/1.2, 1H), 8.02 (d, *J* = 6.1, 1H), 8.03 (d, *J* = 7.9, 1H), 8.16 (d, *J* = 8.4, 1H), 8.81 (m, 1H), 9.34 (s, NH).

Table 6, workup (entries 1-4): the reaction mixture was centrifugated, the resulting pellet was washed with different solvents (washing protocol is indicated below for each entry separately), followed each time by centrifugating. The resulting solid was dissolved in hot THF/MeOH (1:1) and was filtered at this temp. through a 0.45 µm PTFE frit to give pure product;
entry 1, washing protocol: H_2O, Et_2O (3x), dioxane, Et_2O; LCMS $[M+1]^+$ = 674/676, $[M–1]^–$ = 672/674; d (d_6-DMSO) = 2.50 (m, 4H), 2.78 (t, *J* = 5.7, 2H), 3.59 (m, 4H), 3.96 (s, 3H), 4.28 (t, *J* = 5.7, 2H), 7.28 (s, 1H), 7.45 (dd, *J* = 8.6/1.8, 1H), 7.57-7.64 (m, 2H), 7.65 (dd, *J* = 8.9/2.3, 1H), 8.05-8.11 (m, 2H), 8.12 (d, *J* = 2.3, 1H), 8.68 (s, 1H), 9.04 (s, NH), 9.29 (s, NH), 12.26 (br, NH);
entry 2, washing protocol: dioxane, Et_2O (3x), H_2O (2x); LCMS $[M+1]^+$ = 672/674, $[M–1]^–$ = 670/672; d (d_6-DMSO) = 1.70 (m, 4H), 2.00 (quint, *J* = 6.6, 2H), 2.50 (m, 4H), 2.59 (t, *J* = 6.6, 2H), 3.95 (s, 3H), 4.20 (t, *J* = 6.6, 2H), 7.23 (s, 1H), 7.43 (dd, *J* = 8.6/1.7, 1H), 7.57-7.63 (m, 2H), 7.66 (dd, *J* = 8.8/2.3, 1H), 8.04-8.09 (m, 2H), 8.13 (d, *J* = 2.3, 1H), 8.66 (s, 1H), 9.03 (s, NH), 9.31 (s, NH), 12.20 (br, NH);
entry 3, washing protocol: dioxane, Et_2O (3x), H_2O (2x); LCMS $[M+1]^+$ = 672/674; d (d_6-DMSO) = 1.71 (m, 4H), 1.99 (quint, *J* = 6.8, 2H), 2.50 (m, 4H), 2.63 (t, *J* = 6.8, 2H), 3.97 (s, 3H), 4.22 (t, *J* = 6.8, 2H), 7.26 (s, 1H), 7.48 (dd, *J* = 8.7/2.0, 1H), 7.58-7.69 (m, 3H), 8.09-8.15 (m, 3H), 8.71 (s, 1H), 8.99 (s, NH), 9.22 (s, NH), 12.12 (br, NH);
entry 4, washing protocol: dioxane, H_2O, dioxane, Et_2O; LCMS $[M+1]^+$ = 561/563, $[M–1]^–$ = 559/561; d (d_6-DMSO) = 3.96 (s, 3H), 7.09 (s, 1H), 7.44 (dd, *J* = 8.7/2.0, 1H), 7.57-7.63 (m, 2H), 7.67 (dd, *J* = 8.8/2.4, 1H), 8.04-8.10 (m, 2H), 8.13 (d, *J* = 2.4, 1H), 8.59 (s, 1H), 9.22 (s, NH), 9.53 (s, NH), 11.41 (br, NH).

***N*-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazolin-4-yl)-6-nitrobenzo[*d*]oxazol-2-amine (19)**, workup E, the product crystallized from MeOH/Et_2O; LCMS $[M+1]^+$ = 494, $[M–1]^–$ = 492; d (d_6-DMSO) = 1.95 (quint, *J* = 6.6, 2H), 2.18 (s, 3H), 2.31-2.53 (m, 8H), 3.96 (s, 3H), 4.22 (t, *J* = 6.6, 2H), 7.27 (s, 1H), 7.66 (d, *J* = 8.7, 1H), 7.79 (s, 1H), 8.14 (s, 1H), 8.22 (dd, *J* = 8.7/2.3, 1H), 8.42 (d, *J* = 2.3, 1H), 8.55 (s, 1H).

products Scheme 2, workup: the reaction mixture was centrifugated, the resulting pellet was washed with different solvents (washing protocol is indicated below for each compound separately), followed each time by centrifugating;
6-chloro-*N*-(6,7-dimethoxyquinazolin-4-yl)benzo[*d*]thiazol-2-amine (21, X = Cl), washing protocol: MeOH, H_2O (2x), MeOH, Et_2O; LCMS $[M+1]^+$ = 373/375, $[M–1]^–$ = 371/373; d (d_6-DMSO) = 3.96 (s, 3H), 3.97 (s, 3H), 7.28 (s, 1H), 7.44 (dd, *J* = 8.6/2.1, 1H), 7.70 (d, *J* = 8.6, 1H), 8.09 (d, *J* = 2.1, 1H), 8.13 (s, 1H), 8.73 (s, 1H), 12.45 (br, NH);
6-bromo-*N*-(6,7-dimethoxyquinazolin-4-yl)benzo[*d*]thiazol-2-amine (21, X = Br), washing protocol: dioxane, H_2O (2x), Et_2O (3x); LCMS $[M+1]^+$ = 417/419, $[M–1]^–$ = 415/417; d (d_6-DMSO) = 3.95 (s, 3H), 3.96 (s, 3H), 7.27 (s, 1H), 7.56 (dd, *J* = 8.6/2.0, 1H), 7.63 (d, *J* = 8.6, 1H), 8.12 (s, 1H), 8.22 (d, *J* = 2.0, 1H), 8.73 (s, 1H), 12.44 (br, NH);
***N*-(6,7-dimethoxyquinazolin-4-yl)-6-(4-methylpiperazin-1-yl)benzo[*d*]thiazol-2-amine (23)**, washing protocol: dioxane, H_2O (2x), CH_2Cl_2; the resulting solid was dissolved in hot THF and was filtered at this temp. through a 0.45 µm PTFE frit to give pure product; LCMS $[M+1]^+$ = 437, $[M–1]^–$ = 435; d (d_6-DMSO) = 2.23 (s, 3H), 2.50 (m, 4H), 3.16 (m, 4H), 3.95

(s, 3H), 3.96 (s, 3H), 7.12 (d, *J* = 8.8, 1H), 7.27 (s, 1H), 7.48 (s, 1H), 7.57 (d, *J* = 8.8, 1H), 8.11 (s, 1H), 8.69 (s, 1H), 12.21 (br, NH).

Table 7; workup: mixtures were filtered through a pad of silica gel, rinsed with CH_2Cl_2/MeOH 5:1, and the filtrate was concd and purified by prep. HPLC (RP18); within ^1H NMR spectra, *ortho* protons of the aromatic unit attached to the piperidine appeared as extremely broad signals, due to conformational changes within the piperidine unit (indicated as "very br");
entry 1, LCMS $[M+1]^+$ = 561; d ($CDCl_3$) = 2.10 (br, 2H), 2.26 (br, 2H), 2.93 (br, 2H), 3.19 (br, 1H), 3.31 (br, 4H), 3.64 (d, *J* = 11.8, 2H), 3.84, 3.89 (each s, 3H), 4.00, 4.10 (br, together 4H), 6.4-6.9 (very br, 2H), 6.81 (d, *J* = 8.7, 1H), 7.07-7.13 (m, 2H), 7.13 (s, 1H), 7.37 (t, *J* = 7.9, 1H), 7.90 (s, 1H);
entry 2, LCMS $[M+1]^+$ = 531; d ($CDCl_3$) = 2.24 (br, 4H), 2.80 (br, 2H), 3.20 (br, 1H), 3.32 (br, 4H), 3.64 (br, 2H), 3.89 (s, 3H), 3.99, 4.12 (br, together 4H), 6.8-7.2 (very br, 1H), 6.90-6.98 (m, 2H), 7.07-7.13 (m, 3H), 7.13 (s, 1H), 7.37 (t, *J* = 7.9, 1H), 7.90 (s, 1H);
entry 3, LCMS $[M+1]^+$ = 559; d ($CDCl_3$) = 2.41 (br, 4H), 3.32 (br, 7H), 3.71 (br, 2H), 4.02 (br, 4H), 4.24 (s, 4H), 6.89 (d, *J* = 8.6, 1H), 6.95-7.30 (very br, 2H), 7.07-7.13 (m, 2H), 7.13 (s, 1H), 7.37 (t, *J* = 8.0, 1H), 7.91 (s, 1H);
entry 4, LCMS $[M+1]^+$ = 545; d ($CDCl_3$) = 2.31 (br, 4H), 3.02 (br, 2H), 3.23 (br, 1H), 3.32 (br, 4H), 3.64 (d, *J* = 11.6, 2H), 4.02, 4.08 (br, together 4H), 5.95 (s, 2H), 6.4-7.2 (very br, 2H), 6.77 (d, *J* = 8.0, 1H), 7.07-7.13 (m, 2H), 7.13 (s, 1H), 7.37 (t, *J* = 7.9, 1H), 7.90 (s, 1H);
entry 5, LCMS $[M+1]^+$ = 569; d ($CDCl_3$) = 1.99 (qd, *J* = 11.8/3.9, 2H), 2.27 (dd, *J* = 12.9/2.4, 2H), 3.02 (td, *J* = 11.8/2.4, 2H), 3.23 (tt, *J* = 11.8/3.9, 1H), 3.31 (br, 4H), 3.89 (d, *J* = 12.9, 2H), 4.00, 4.09 (br, together 4H), 6.98 (d, *J* = 8.7, 2H), 7.08 (d, *J* = 8.0, 1H), 7.12 (d, *J* = 8.0, 1H), 7.14 (s, 1H), 7.37 (t, *J* = 8.0, 1H), 7.49 (d, *J* = 8.7, 2H), 7.90 (s, 1H);
entry 6, LCMS $[M+1]^+$ = 585; d ($CDCl_3$) = 2.34, 2.44 (br, together 4H), 3.14 (br, 2H), 3.32 (br, 5H), 3.76 (d, *J* = 13.4, 2H), 4.04 (br, together 4H), 7.0-7.4 (very br, 2H), 7.08-7.14 (m, 2H), 7.14 (s, 1H), 7.21 (d, *J* = 8.2, 2H), 7.38 (t, *J* = 8.0, 1H), 7.91 (s, 1H);
entry 7, LCMS $[M+1]^+$ = 552.

Additional References and Notes

[S1] This attempt was expected to have only a minor chance of success due to the fact that Cs_2CO_3 was found to be essential for the preparation of *N*-arylazoles and stronger bases might hamper reaction progress within this catalytic system by resulting in too high a concentration of azolyl anions; cf. ref.[17]

[S2] Comparable difficulties were reported for the Cu catalyzed conversion of 2-methylindole with 2-bromotoluene or 2-bromoanisole, which failed with the former and proceeded quite sluggishly with the latter, see ref.[8] With 3,5-dimethylpyrazole, *N*-arylations were reported only using unhindered aryliodides neat as solvent, see. ref.[34]

[S3] T. Ibata, Y. Isogami, J. Toyoda, *Bull. Chem. Soc. Jpn*. **1991**, *64*, 42-49.

[S4] M. L. Quan, P. Y. S. Lam, Q. Han, D. J. P. Pinto, M. Y. He, R. Li, C. D. Ellis, C. G. Clark, C. A. Teleha, J.-H. Sun, R. S. Alexander, S. Bai, J. M. Luettgen, R. M. Knabb, P. C. Wong, R. R. Wexler, *J. Med. Chem*. **2005**, *48*, 1729-1744.

[S5] W. J. Smith III, J. S. Sawyer, *Tetrahedron Lett*. **1996**, *37*, 299-302.

[S6] L. Jeppesen (Novo Nordisk), WO 95/21842, **1995**; *Chem. Abstr*. **1996**, *124*, 8850.

[S7] a) K. M. Shubin, V. A. Kuznetsov, V. A. Galishev, *Tetrahedron Lett*. **2004**, *45*, 1407-1408; b) G. J. Atwell, G. W. Rewcastle, W. A. Denny, B. F. Cain, B. C. Baguley, *J. Med. Chem*. **1984**, *27*, 367-372; c) G. J. Atwell, G. W. Rewcastle, B. C. Baguley, W. A. Denny, *J. Med. Chem*. **1987**, *30*, 652-658; d) C.Garino, N. Pietrancosta, Y. Laras, V. Moret, A. Rolland, G. Quelever, J.-L. Kraus, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1995-1999; e) B. Ye, S. Bauer, B. O. Buckman, A. Ghannam, B. D. Griedel, S.-K. Khim, W. Lee, K. L. Sacchi, K. J. Shaw, A. Liang, Q. Wu, Z. Zhao, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3361-3365.

[S8] G. J. Atwell, B. C. Baguley, G. J. Finlay, G. W. Rewcastle, W. A. Denny, *J. Med. Chem*. **1986**, *29*, 1769-1776.

[S9] J. F. Bunnett, R. E. Zahler, *Chem. Rev*. **1951**, *49*, 273-412.

[S10] a) S. Maiorana, C. Baldoli, P. del Buttero, M. di Ciolo, A. Papagni, *Synthesis* **1998**, 735-738; b) F. Moulines, M. Kalam-Alami, V. Martinez, D. Astruc, *J. Organomet. Chem*. **2002**, *643-644*, 125-129.

[S11] a) J. Ji, T. Li, W. H. Bunnelle, *Org. Lett.* **2003**, *5*, 4611-4614; b) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem*. **2005**, *117*, 1395-1399; *Angew. Chem. Int. Ed. Engl*. **2005**, *44*, 1371-1375; c) T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemiere, R. Dommisse, *Tetrahedron* **2001**, *57*, 7027-7034; d) J. Cheng, M. L. Trudell, *Org. Lett.* **2001**, *3*, 1371-1374.

[S12] J.-S. Yang, Y.-H. Lin, C.-S. Yang, *Org. Lett.* **2002**, *4*, 777-780.