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

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**Abstract:** The application of palladium- and copper-catalyzed reactions for the aromatic amination of pharmacologically relevant scaffolds is investigated. The focus is set on the scope of several protocols for the introduction of amines of broad structural diversity, allowing for the synthesis of numerous derivatives of one biological hit structure for screening in biological assay systems. Thus, attaining optimized yields and TONs had not a major priority, most important were practical aspects, that is no further purification and drying of reagents and solvents had to be envisaged, ideally only a few transition metal-based protocols had to be applied for synthesizing structurally diverse compounds in sufficient amounts (several milligrams) for screening without any fine-tuning of conditions and catalytic systems.

**Keywords:** amination; copper; cross-coupling; homogeneous catalysis; medicinal chemistry; palladium

## Introduction

Starting with almost simultaneous landmark publications from Hartwig's and Buchwald's laboratories,[1] numerous articles on transition metal-mediated aromatic amination reactions of aryl halides were published during the past decade by several working groups on almost every aspect of this reaction type.[2,3] Major focus was laid primarily on Pd-catalyzed reactions. The use of catalytic copper(I) species, however, accrued relevance due to systematic substrate evaluation with a 4-year-onset,[4] again triggered by work of Buchwald's group.[5] In the meantime, the synthetic chemist has the choice of several palladium- and copper-based amination protocols which can display complementary advantages for different conversions (i.e., switching chemoselectivity),[6–8] and even a few procedures are now available using nickel species.[9] Most of the procedures elaborated had in common that research was performed under ideal conditions for transition metal catalysis: standard set-ups for drying of solvents were used, substrates and agents were assembled in a dry-box or at least the bulk of the base was stored under an inert atmosphere, starting amines were distilled or purified by passing over a column of alumina, or – in several cases – ligands or catalysts were freshly prepared to guarantee a certain quality.

As amine-substituted aromatics and heteroaromatics represent desirable frameworks in medicinal chemistry, aromatic amination protocols had to survive scrutiny under "non-optimal" reaction conditions for transition metal catalysis as usually encountered in R&D laboratories to prove their general applicability. Generally that is, solvents and reagents are used as bought without further drying or purification, and weighing procedures are performed in normal atmosphere. Furthermore, substrates are usually substituted in a more complex way than those carefully chosen as test substrates for methodical evaluations of a technique. As time is an important factor in pharmaceutical research, extensive investigations into subtle changes of conditions (different ligand derivatives, inorganic bases, Pd sources within one given method, concentration, etc.) for obtaining optimized yields are usually not feasible. Thus, a most general and simple protocol was required, with a broad application for the quick synthesis of small libraries with a defined structural diversity. For reasons of simplicity and time saving, certain protocols including pre-mixing of reagents or a certain order of assembling of all ingredients were not followed. In most cases, slightly more transition metal catalyst was applied than published within the original protocols, since with no further purification of solvents and amines, turnover numbers (TONs) were expected to be lower as compared to

the literature. Furthermore, it was not the major focus to decrease Pd quantities to establish the high catalytic potential of a method, but to obtain significant amounts of product for biological screening without the necessity of optimizing yields.[10,11]

The advantages of transition metal-catalyzed aromatic amination reactions over other chemical ways of amine introduction are supposed to be manifold:

a) the broad methodical work published offers a procedure for the coupling of almost any amine, that is, anilines, aliphatic amines, amides, N-heterocycles, carbamates, etc.;

b) by relying on differently active leaving groups (e.g., Cl *vs.* Br) at the aromatic reaction partner, a stepwise introduction of two different substituents can be achieved with clearly defined regioselectivity;

c) several different electronic conditions are tolerated within the aromatic ring, which is favorable over amine introduction by $S_NAr$-type reactions, which usually call for nitro substitution or at least substitution with strongly electron-withdrawing groups located in *ortho* or *para* position to the leaving group, or a nitrogen within a heterocyclic framework.

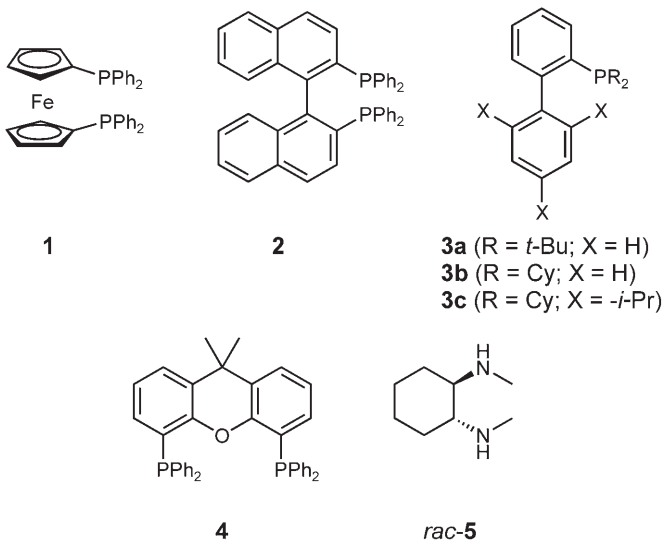



**Figure 1.** Selection of efficient ligands for aromatic amination reactions.

## Results and Discussion

### Two-Fold Aromatic Amination of 2,5-Dihalogenated Arenes

Starting with the synthesis of a new series of serotonin receptor ligands,[12] a 2,4- and 2,5-diamination pattern of nitroarenes was envisaged to be installed by two-fold aromatic amination. Usually, 2,4-diaminated nitroarenes have been realized by subsequent $S_NAr$ reactions on the 2,4-dihalogenated analogues (for a discussion, see Supporting Information). However, with a focus on scaffold variations including the replacement of the nitro functionality of these substrates by other polar "head groups", an $S_NAr$ approach was not feasible anymore – especially not for a 2,5-substitution pattern, with the second leaving group being located in an unfavorable position for $S_NAr$ chemistry.

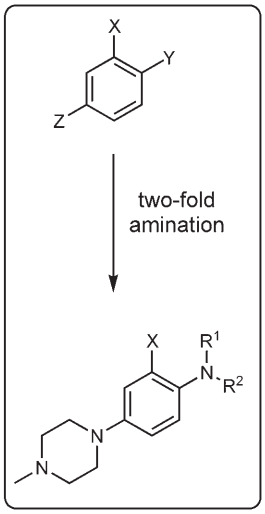
A first method evaluation was performed on 1-bromo-4-chloro-2-nitrobenzene (Table 1), amination of which with benzylamine (entry 1) should occur on the bromine site with excellent selectivity over the chlorine site.[13] Even though protocols utilizing dialkylphosphino-biphenyl ligands (like **3**, Figure 1) seemed to be among the most active Pd/ligand systems for aminations of bromo- and chloroarenes,[14] with good chemoselectivities having been reported,[10,15] they were not applied here for substrates bearing both leaving groups simultaneously. Given the excellent TONs of this catalytic system as were reported, amination reactions might not have stopped upon amination of all of the bromine sites, with generally an excess of amine being present to avoid double arylation of primary amines. Thus, catalytic systems were chosen which were known to leave chloroarenes unaltered: transformations were conducted using DPPF (**1**, method A) and BINAP (**2**, method B) as chelating ligands, according to Hartwig's and Buchwald's early procedures for the amination of bromoarenes.[13,16]

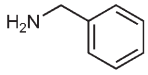
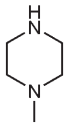
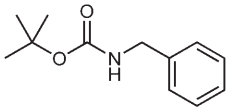
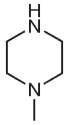
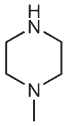
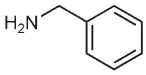
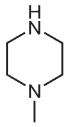
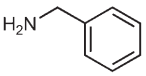
Despite the fact that nitroarenes are usually classified as base-sensitive substrates, rarely tolerating strong bases like sodium alkoxides in amination reactions,[2,3,13,17] the DPPF-based procedure resulted in 25% isolated yield. On the other hand, with BINAP (**2**) as ligand, $Cs_2CO_3$ had better been chosen according to the recommendation in the literature,[13] and – as cited – only decomposition of starting material was observed with NaO-*t*-Pent.[18] In general, sodium *tert*-pentoxide was used throughout our work rather than sodium *tert*-butoxide, as *tert*-pentoxides were mentioned by Nolan and co-workers to be somewhat superior to the corresponding *tert*-butoxides under certain amination conditions, most likely due to their enhanced solubility in organic solvents.[19] Furthermore, sodium *tert*-pentoxide was expected to be less hygroscopic than the corresponding butoxide,[20] which, of course, would result in a significant advantage over time as all bases were stored on the shelf without further precautions.

For additional evaluation of the most suitable procedures, protocols were applied for the cross-coupling of benzylamine with 1-bromo-4-chloro-2-nitrobenzene (entry 1), in which water was employed as (co-)solvent (methods C1 and D1), thus eliminating any possible disadvantages due to residual moisture in sol-

**Table 1.** Two-fold amination of 2,5-dihalogenated nitroarenes.




| Entry | X | Y | Z | 1st Amination (at Br site) Amine | Procedure[a] | Yield | 2nd Amination (at Cl site) Amine | Procedure[a] | Yield |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $NO_2$ | Br | Cl |  | A | 25%[b] |  | C2 | --[e] |
| | | | | | B1 | traces[c] | | | |
| | | | | | C1 | 43%[d] | | | |
| | | | | | D1 | 6%[b] | | | |
| | | | | | D2 | traces[c] | | | |
| 2 | $NO_2$ | Br | Cl |  | C3 | --[d] |  | C2 | 82% |
| | | | | | D3 | --[f] | | | |
| | | | | | E1 | --[g] | | | |
| | | | | | F1 | 66% | | | |
| 3 | $CO_2Me$ | Cl | Br |  | A | 38%[h] |  | C4 | 16%[h] |
| 4 | OMe | Cl | Br |  | A | 67% |  | C4 | 85% |

[a] **A**: Ar-Br/amine 1.0:1.1; 0.05 equivs. $(DPPF)PdCl_2$, 0.15 equivs. DPPF (**1**), 1.25 equivs. NaO-*t*-Pent, THF (2 mL mmol$^{-1}$ Ar-Br), 100 °C, 4 h; **B1**: Ar-Br/amine 1.0:1.1; 0.01 equivs. $Pd_2dba_3$, 0.03 equivs. BINAP (**2**), 1.4 equivs. NaO-*t*-Pent, toluene (2 mL mmol$^{-1}$ Ar-Br), 80 °C, 20 h; **C1**: Ar-Br/amine 1.0:1.1; 0.01 equivs. $Pd_2dba_3$, 0.04 equivs. $(biph)P(t\text{-}Bu)_2$ **3a**, 1.5 equivs. KOH, $H_2O$ (0.6 mL mmol$^{-1}$ Ar-Br), 60 °C, 20 h; **C2**: Ar-Cl/amine 1.0:1.3; 0.10 equivs. $Pd(OAc)_2$, 0.20 equivs. $(biph)P(t\text{-}Bu)_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (2 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **C3**: Ar-Br/amine 1.0:1.1; 0.03 equivs. $Pd_2dba_3$, 0.12 equivs. $(biph)P(t\text{-}Bu)_2$ **3a**, 1.4 equivs. $Cs_2CO_3$, toluene (1.2 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h; **C4**: Ar-Cl/amine 1.0:1.3; 0.05 equivs. $Pd_2dba_3$, 0.20 equivs. $(biph)P(t\text{-}Bu)_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene (2 mL mmol$^{-1}$ Ar-Cl), 110 °C, 20 h; **D1**: Ar-Br/amine 1.0:1.05; 0.01 equivs. $Pd_2dba_3$, 0.04 equivs. $P(t\text{-}Bu)_3\text{-}HBF_4$, 0.005 equivs. $(cetyl)NMe_3Br$, 1.5 equivs. KOH in $H_2O$ (45%), toluene (1.2 mL mmol$^{-1}$ Ar-Br), 90 °C, 20 h; **D2**: Ar-Br/amine 1.0:1.05; 0.01 equiv. $Pd_2dba_3$, 0.016 equivs. $P(t\text{-}Bu)_3\text{-}HBF_4$, 1.5 equivs. NaO-*t*-Pent, toluene (1.2 mL mmol$^{-1}$ Ar-Br), r.t., 20 h; **D3**: Ar-Br/amine 1.0:1.1; 0.02 equivs. $Pd_2dba_3$, 0.08 equivs. $P(t\text{-}Bu)_3\text{-}HBF_4$, 1.4 equivs. $NaOPh\cdot 3H_2O$, toluene (3 mL mmol$^{-1}$ Ar-Br), 100 °C, 4 h; **E1**: Ar-Br/amine 1.0:1.1; 0.07 equivs. CuI, 0.14 equivs. *rac*-**5**, 2.0 equivs. $K_2CO_3$, toluene (1 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h; **F1**: Ar-Br/amine 1.0:1.1; 0.03 equivs. $Pd(OAc)_2$, 0.045 equivs. Xantphos (**4**), 1.4 equivs. $Cs_2CO_3$, dioxane (1 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h.

[b] Starting bromoarene detected (LC-MS), some decomposition occurred.

[c] Traces of product and starting bromoarene detected (LC-MS), decomposition occurred.

[d] Starting bromoarene detected/recovered.

[e] Only formation of side product **6** observed (LC-MS).

[f] Traces of product found, starting bromoarene recovered, some decomposition occurred, side product 4-chloro-2-nitro-1-phenoxybenzene isolated.

[g] Starting bromoarene recovered, biaryl **7a** isolated, halogen exchange (I for Br) observed.[24]

[h] Isolated yield for methyl ester; *tert*-pentyl ester formation (transesterification) detected by LC-MS (Me vs. *t*-Pent ca. 3:1, not standardized).

Isolated yields, yields are not optimized; DME = 1,2-dimethoxyethane, monoglyme.

vents used as bought. In this case, the advantages gained by the choice of solvent justified risking side reactions by over-amination as the Pd/ligand systems utilized usually qualify for effective oxidative addition to the chloro-arene bond as well. Interestingly, the best result was achieved applying method C1 (43%), conducted as a modification of the original Buchwald protocol,[6] in which a specialized, highly sterically encumbered dicyclohexylphosphino-biphenyl ligand **3c** had been used (as compared to **3a** in our case), which usually necessitated a certain fine-tuning of conditions for different substrate subtypes. For our purposes

(biph)P(*t*-Bu)$_2$ **3a** was chosen as standard representative of the class of monodentate biphenyl P-ligands through all but one of our respective reactions. This ligand had been introduced by Buchwald within a protocol claimed to be among the most benign amination procedures with respect to generality and scope for amination reactions of chloro- and bromoarenes.[14]

For an application of procedures based on P(*t*-Bu)$_3$, a highly active but air-sensitive (pyrophoric) ligand, the corresponding air-insensitive $HBF_4$ salt was chosen, enabling handling under normal atmosphere.[21] Utilization of KOH in a solvent mixture toluene/water under phase-transfer conditions (method D1) was supposed to be more compatible with base-sensitive functional groups as compared to the application of sodium alkoxides according to the literature (*cf.* also yield of method A *vs.* method C1).[22] For an attempted room temperature amination based on the same catalytic system, NaO-*t*-Pent had to be used in toluene (method D2), as weaker inorganic bases ($K_3PO_4$ or $Cs_2CO_3$) displaying a better compatibility with nitroarenes would have called for elevated reaction temperatures.[17,23] However, in both cases (methods D1 and D2) problems were reported using primary amines other than anilines, and the reactions (entry 1) proceeded accordingly.

Despite the best coupling result of 43% for the amination entry 1 using method C1, the DPPF-based protocol A was chosen for further aminations of bromoarenes although the yield was inferior in this case. The latter method proved to be a more general procedure, however, accompanied by acceptable yields for a more diverse subset of aryl bromide substrates (not shown).[18] Furthermore, this protocol employs the least cost expensive P-ligand among those depicted in Figure 1, resulting in highest reaction rates (max. conversion reached usually upon 3–4 h reaction time) with complete chemoselectivity.

The second amination step on the benzylamino substrate attained (entry 1), that is an exchange of chlorine with *N*-methylpiperazine, was attempted with the ligand (biph)P(*t*-Bu)$_2$ **3a** (method C2) – but only to find side product formation, according to LC-MS maybe a self-dechloro-dimerization to give product **6** (Figure 2), with the benzylic NH of the substrate outperforming piperazine as nucleophile upon deprotonation. For a completion of this sequence, a Boc protection of the benzylamine unit was scheduled, which was not readily achieved on substrate of entry 1 upon first amination due to the electron-withdrawing properties of the *ortho* nitro group. Therefore, a direct incorporation of *N*-Boc-benzylamine was attempted using Pd chemistry as well as a copper-based protocol optimized for the introduction of mainly amides to bromoarenes (method E1).[25] Within the latter method, the detection of biaryl **7a** resulting from a

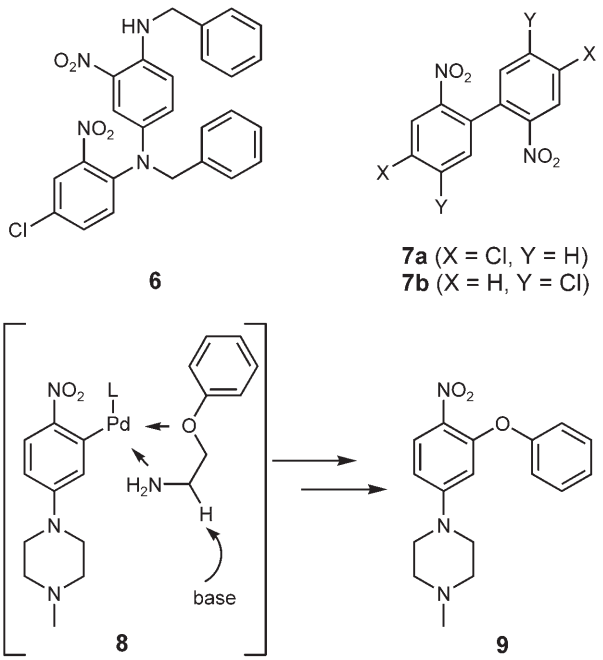



**Figure 2.** Isolated side products from amination reactions of nitroarenes.

non-catalytic Ullmann coupling is indicative of a reaction rate being too slow for the amination process, so that biaryl formation became competitive and used up all the catalytic copper species. Racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (*rac*-**5**, Figure 1) was chosen as standard ligand for copper-based aminations throughout this work according to its advantageous reactivity profile as compared to numerous other diamine ligands elaborated by Buchwald's group.[8,25]

Following a Hartwig protocol for the introduction of primary and secondary *tert*-butyl carbamates to aryl bromides, P(*t*-Bu)$_3$ and sodium phenolate were chosen as reagents,[17,26] the ligand again being used as its $HBF_4$ salt (method D3). The use of (biph)P(*t*-Bu)$_2$ **3a** in this conversion (method C3) was in accordance to an effective amination of several chloroarenes (also nitro-substituted) with oxazolidinones, although it was stated that reactions proceeded quite sluggishly if substrates were equipped with an *ortho* substituent.[27] Eventually, a protocol based on Xantphos (**4**, Figure 1), a ligand highly effective for amination reactions of bromoarenes with weak N-nucleophiles,[28–30] proved to be most effective (method F1, 66% isolated yield). Standard amination at the chlorine site in a second amination step now proceeded smoothly with $K_3PO_4$ as base (entry 2, method C2, 82%).

Another way to circumvent the side product formation as encountered in entry 1, second step, was the exchange of positions of bromine and chlorine within the aromatic substrate and hence an amination with a secondary amine prior to the introduction of a pri-

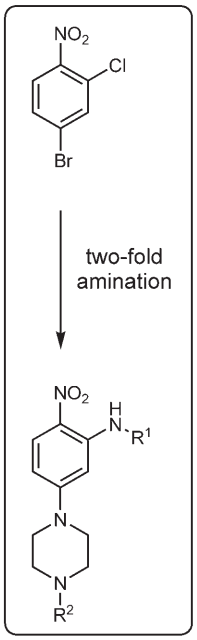
  

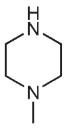
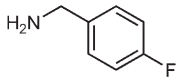
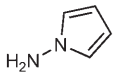
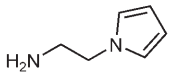
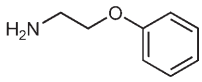
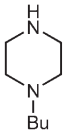
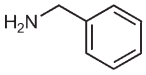
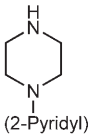
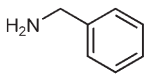
mary amine. This approach was realized for a methyl benzoate (entry 3), and was also necessitated for an anisole substrate (entry 4) since the corresponding 2-bromo-5-chloro-derivative was not commercially available for this head group. Conditions chosen for the two-fold amination sequence seemed to be superior for the electron-rich substrate (entry 4 *vs.* entry 3), which might simply be explained by a poor substrate compatibility of the ester with NaO-*t*-Pent, though. For the first amination of methyl benzoate (entry 3) at the bromine site, this argument seemed to be a valid explanation for the moderate yield obtained, as a similar conversion of a structural isomer of this ester (Table 4, entry 18) could be improved significantly when switching to a BINAP (**2**)/$Cs_2CO_3$ system (*vide infra*). The second amination using (biph)P(*t*-Bu)$_2$ **3a** – that is, in an *ortho* position to the head group at the chlorine site – however, was shown later to give superior results using NaO-*t*-Pent as compared to $K_3PO_4$ (*cf.* Table 4, entries 18 and 19) in spite of the potential for decomposition and/or transesterification, with a stronger base being required to allow for an active catalytic cycle.

## Two-Fold Amination of 2,4-Dihalogenated Nitroarenes

Within the 2,4-dihalogenated substrate series, the 4-substituent was usually chosen to become *N*-methylpiperazine, so that a most convergent synthetic strategy would start with installing this substituent first, thus requiring the bromine in said position. Several structurally diverse products obtained by such a two-fold

**Table 2.** Two-fold amination of 2,4-dihalogenated nitroarenes.




| Entry | 1st Amination (at Br site) Amine | Procedure[a] | Yield | 2nd Amination (at Cl site) Amine | Procedure[a] | Yield |
|---|---|---|---|---|---|---|
| 5 |  | A | 37%[b] |  | C2[c,d] | 7% |
| 6 | | | |  | C2 | 69% |
| 7 | | | |  | C2<br>C4 | 6%[e]<br>15%[d] |
| 8 | | | |  | C2<br>C4 | 26%[d]<br>6%[f] |
| 9 |  | A | 36% |  | C4 | 2% |
| 10 |  | A | 38% |  | C4 | 1% |

[a] **A**: Ar-Br/amine 1.0:1.1; 0.05 equivs. (DPPF)$PdCl_2$, 0.15 equivs. DPPF (**1**), 1.25 equivs. NaO-*t*-Pent, THF (2 mL mmol$^{-1}$ Ar-Br), 100 °C, 4 h; **C2**: Ar-Cl/amine 1.0:1.3; 0.10 equivs. $Pd(OAc)_2$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (2 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **C4**: Ar-Cl/amine 1.0:1.3; 0.05 equivs. $Pd_2dba_3$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene (2 mL mmol$^{-1}$ Ar-Cl), 110 °C, 20 h.

[b] Formation of aryl (*tert*-pentyl) ether observed (< 3 %), *cf.* also ref.[14]

[c] Ar-Cl/amine 1.0:1.1; 0.03 equivs. $Pd(OAc)_2$, 0.06 equivs. (biph)P(*t*-Bu)$_2$ **3a**.

[d] Major amounts of starting chloroarene unaltered (LC-MS).

[e] 35 % isolated side product of Heck reaction, starting chloroarene recovered.

[f] 15 % isolated side product **9**.

Isolated yields, yields are not optimized.

amination sequence are depicted in Table 2, following the final procedure selection made for the 2-bromo-5-chloro series (Table 1, entry 1). The first amination step was accomplished with different piperazines in mediocre yields (24–38%, DPPF-based protocol, NaO-*t*-Pent as base, method A). (Biph)P(*t*-Bu)$_2$-based procedures (C2 and C4) allowed for the introduction of benzylamines (Table 2, entries 5, 9 and 10), *N*-aminopyrroles (entry 6) and 2-substituted ethylamines (entries 7 and 8) in the 2-position. In general, amination reactions of 2-chloronitroarenes proceeded quite sluggishly, either due to only very low TONs achieved with $K_3PO_4$ as base with the major amount of starting chloroarene still being present unaltered (entries 5 and 8), or due to decomposition encountered with the stronger base NaO-*t*-Pent[13,17] (entries 7–10) – which is in good agreement with literature data.[14]

Amination with *N*-aminopyrrole as an aniline analogue succeeded with quite an excellent result (entry 6, 69%), not even encountering Heck-type side reactions as with the substrate of entry 7, which could be subdued in the latter case by switching from $K_3PO_4$ (method C2) to the stronger base NaO-*t*-Pent (C4). With *N*-(2-aminoethyl)pyrrole (entry 7), utilization of a stronger base most likely enhanced or accelerated the formation of a palladium-amido complex within the catalytic cycle, thus rendering C–N bond formation competitive to Heck-type C–C coupling. A *vice versa* phenomenon was observed with 2-phenoxyethylamine as substrate (entry 8), with which a major side reaction occurred when NaO-*t*-Pent was utilized, giving rise to diaryl ether **9**. For the formation of the latter, a β-elimination in species **8** was postulated (Figure 2), resulting in an intermediary (aryl)Pd(phenoxide) species. This side reaction indeed became less competitive when the weaker base $K_3PO_4$ was applied, and a moderate yield of 26% was achieved without any formation of diaryl ether **9**.

As there are only a few examples of amination reactions on chloroarenes with weak N-nucleophiles like amides, carbamates or N-heterocycles using Pd or Cu catalysis,[17,25,27,32] a less favorable amination sequence had to be chosen for the introduction of these amines in which divergence was already introduced within the first amination step at the 2-bromine site followed by introduction of *N*-methylpiperazine at the chlorine site (Table 3). For pyridazinone, the necessity of such a change in strategy was confirmed by its failed introduction into a 2-chloro-4-(*N*-methylpiperazin-1-yl)-nitrobenzene using ligand **3a** (method C4).

Earlier results had shown a final introduction of benzylamines in the 2-position with chlorine as leaving group to give low yields (<10%, Table 2, entries 5, 9 and 10), but – in contrast – an attachment of Boc-protected benzylamine at the 2-bromine position to be an excellent alternative (Table 1, entry 2). Therefore, the latter sequence was conducted likewise with the 2,4-disubstituted nitroarenes to give quite good yields (entries 11 and 12). Some structural variety was attained with the introduction of N-heterocycles, even though yields were quite poor. In these cases (entries 13 and 14), a Cu-based protocol (method E2)[8] was superior to palladium chemistry using P(*t*-Bu)$_3$ as ligand,[17] again as its $HBF_4$ salt (method D4). With pyrroles as N-nucleophiles and Pd catalysis, Heck-type arylation at a carbon atom of the pyrrole became dominant (entry 13), which is in accordance – but still with surprising preference in our case – with literature data for corresponding arylations of indoles with *ortho* substituted aryl bromides.[8,17] Such a side reaction[33] could be excluded when 3,5-dimethylpyrazole was used (entry 14), but yields from the Pd-catalyzed conversion were still poor (7%). Somewhat enhanced yields were obtained for the *N*-arylation of pyrroles and pyrazoles using copper chemistry, standard protocols of which were originally established for aryl iodides as substrates,[7] and have been adapted here according to further progress achieved for the *N*-arylation of indoles.[8,34] For Cu-based reactions of entries 13 and 14, desired conversions were hampered by significant side product formation (biaryl formation, halogen exchange).

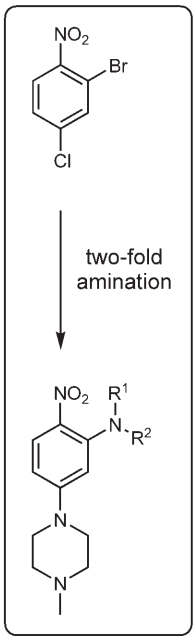
A second amination step with *N*-methylpiperazine using our standard Pd protocols C2 or C4, was only successful with the latter procedure to give 7% and 30% for the pyrrole and pyrazole derivatives, respectively (entries 13 and 14). For benzamides (entries 15 and 16) and pyridazinone (entry 17), Pd in combination with Xantphos (**4**) proved to be the method of choice (method F1).[28] Reaction of the latter resulted in an incomplete conversion and a poor yield, though, with $K_3PO_4$ being slightly favorable over $Cs_2CO_3$ as base (entry 17).[35] Final amination with *N*-methylpiperazine proceeded smoothly in all three cases with decent yields ranging from 48 to 76% (entries 15–17 and also 11 and 12).

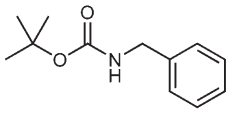
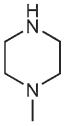
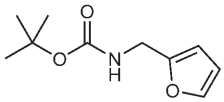
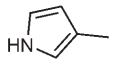
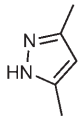
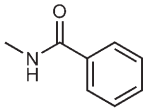
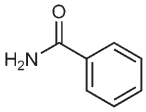
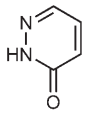
Despite the fact that, in some instances, a copper-based procedure represented the only way to attain significant amounts of product (entries 13 and 14), yields were generally unsatisfactory. In all Cu-catalyzed amination attempts on 2-bromonitroarenes (Table 1, entry 2; Table 3, entries 13–15), a bromine-iodine exchange[24] and a formation of biaryl **7** was observed, the latter resulting from a competing non-catalytic Ullmann coupling, which would result in loss of catalytically active copper in the appropiate oxidation state.

Given the occurring side reactions with 2-bromonitroarenes in these conversions and the fact that sterically demanding pyrazoles, like 3,5-dimethylpyrazole, were stated to be only viable substrates for *N*-arylation with unhindered aryl iodides used neat as solvent[34] – which, however, would not have been a fea-

**Table 3.** Two-fold amination of 2,4-dihalogenated nitroarenes.




| Entry | 1st Amination (at Br site) Amine | Procedure[a] | Yield | 2nd Amination (at Cl site) Amine | Procedure[a] | Yield |
|---|---|---|---|---|---|---|
| 11 |  | F1 | 51% |  | C2 | 59% |
| 12 |  | F1 | 31% | | C2 | 51% |
| 13 |  | D4<br>E2 | traces[b]<br>14%[d] | | C2<br>C4 | --[c]<br>7%[e] |
| 14 |  | D4<br>E2 | 7%<br>18%[f] | | C4 | 30%[e] |
| 15 |  | E1<br>F1[g] | --[d]<br>65%[h] | | C2 | 76% |
| 16 |  | F1[g] | 20%[h] | | C2 | 48% |
| 17 |  | F1[g]<br>F2 | 4%[i,k]<br>8%[i] | | C2 | 62% |

[a] **C2**: Ar-Cl/amine 1.0:1.3; 0.10 equivs. $Pd(OAc)_2$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (2 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **C4**: Ar-Cl/amine 1.0:1.3; 0.05 equivs. $Pd_2dba_3$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene (2 mL mmol$^{-1}$ Ar-Cl), 110 °C, 20 h; **D4**: Ar-Br/amine 1.0:1.2; 0.04 equivs. $Pd_2dba_3$, 0.08 equivs. P(*t*-Bu)$_3$-$HBF_4$, 1.4 equivs. $Cs_2CO_3$, toluene (3 mL mmol$^{-1}$ Ar-Br), 100 °C, 20 h; **E1**: Ar-Br/amine 1.0:1.1; 0.07 equivs. CuI, 0.14 equivs. *rac*-**5**, 2.0 equivs. $K_2CO_3$, toluene (1 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h; **E2**: Ar-Br/amine 1.0:1.2; 0.10 equiv. CuI, 0.30 equivs. *rac*-**5**, 2.1 equivs. $K_3PO_4$, toluene (1 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h; **F1**: Ar-Br/amine 1.0:1.1; 0.03 equivs. $Pd(OAc)_2$, 0.045 equivs. Xantphos (**4**), 1.4 equivs. $Cs_2CO_3$, dioxane (1 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h; **F2**: Ar-Br/amine 1.0:1.1; 0.02 equivs. $Pd_2dba_3$, 0.06 equivs. Xantphos (**4**), 1.4 equivs. $K_3PO_4$, dioxane (1 mL mmol$^{-1}$ Ar-Br), 100 °C, 20 h.

[b] Side products of Heck reaction isolated, starting bromoarene recovered.

[c] No conversion, only starting chloroarene detectable.

[d] Starting bromoarene recovered, biaryl **7b** isolated, halogen exchange (I for Br) observed.[24]

[e] No starting chloroarene detectable.

[f] Starting bromoarene recovered, biaryl **7b** and biaryl of reductive coupling on Cl site of nitroarene isolated, minor quantities of **5** *N*-arylated (detected by LC-MS), halogen exchange (I for Br) observed.[24]

[g] Reaction conducted at 100 °C.

[h] LC-MS indicated complete conversion for both reactions, differences in yields due to work-up.

[i] Starting bromoarene detected (LC-MS).

[k] NMR indicated side product of *O*-arylation of pyridazinone.

Isolated yields, yields are not optimized.

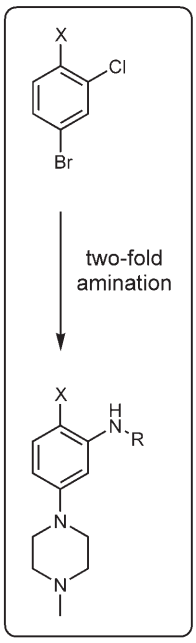
sible alternative with 2-bromo-4-chloro-1-nitrobenzene – an 18% yield in entry 14 seems to be quite excellent. In this case, the observed halogen exchange might have been an important factor favoring product formation.[36]

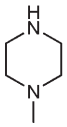
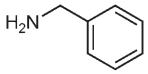
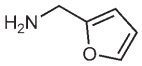
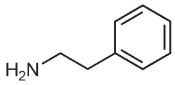
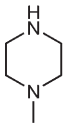
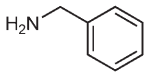
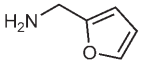
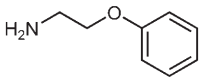
## Two-Fold Amination of 2,4-Dihalogenated Non-Nitroarenes

Upon exchange of the nitro head group for other electron-withdrawing functionalities, like carboxylic

**Table 4.** Two-fold amination of 2,4-dihalogenated benzoic esters and benzonitriles.




| | | 1st Amination (at Br site) | | | 2nd Amination (at Cl site) | | |
|---|---|---|---|---|---|---|---|
| Entry | X | Amine | Procedure[a] | Yield | Amine | Procedure[a] | Yield |
| 18 | $CO_2Me$ |  | A | 38%[b] |  | C2 | 2%[c] |
| | | | B2 | 87% | | C4 | 38% (9%)[d] |
| 19 | | | | |  | C2 | 9%[c] |
| | | | | | | C4 | 21% (4%)[d] |
| 20 | | | | |  | C4 | 30%[e] |
| 21 | CN |  | A | 60% |  | C4 | 62% |
| 22 | | | | |  | C4 | 54% |
| 23 | | | | |  | C2 | 43% |

[a] **A**: Ar-Br/amine 1.0:1.1; 0.05 equivs. $(DPPF)PdCl_2$, 0.15 equivs. DPPF (**1**), 1.25 equivs. NaO-*t*-Pent, THF (2 mL mmol$^{-1}$ Ar-Br), 100 °C, 4 h; **B2**: Ar-Br/amine 1.0:1.1; 0.03 equivs. $Pd(OAc)_2$, 0.045 equivs. BINAP (**2**), 1.4 equivs. $Cs_2CO_3$, toluene (2 mL mmol$^{-1}$ Ar-Br), 100 °C, 20 h; **C2**: Ar-Cl/amine 1.0:1.3; 0.10 equivs. $Pd(OAc)_2$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (2 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **C4**: Ar-Cl/amine 1.0:1.3; 0.05 equivs. $Pd_2dba_3$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene (2 mL mmol$^{-1}$ Ar-Cl), 110 °C, 20 h.

[b] Side product formation detected by LC-MS: methyl ester vs. *tert*-pentyl ester *vs.* aryl (*tert*-pentyl) ether 5:2:1 (not standardized).

[c] Major amounts of starting chloroarene unaltered.

[d] Value given in parentheses accounts for additionally isolated product as *tert*-pentyl ester.

[e] Isolated yield for methyl ester; *tert*-pentyl ester formation detected by LC-MS (Me *vs.* *t*-Pent *ca.* 3:1, not standardized). Isolated yields, yields are not optimized.

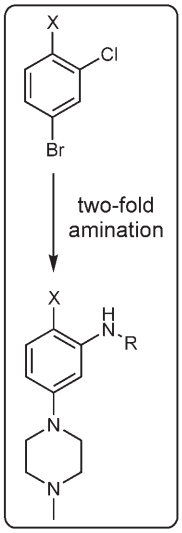
ester or nitrile groups (Table 4), or electron-donating alkoxy groups (Table 5), amination reactions proceeded generally in good yields for both the first and the second amination step. For the introduction of *N*-methylpiperazine into methyl benzoate (entry 18), a milder variant using BINAP (**2**) and $Cs_2CO_3$ (method B2) proved to be superior over DPPF (**1**)/NaO-*t*-Pent, giving rise to more than twice the product outcome, which is in good accordance with literature statements.[13,14,16,17] In the second amination reaction with benzyl- and furfurylamine (entries 18 and 19), however, $K_3PO_4$ was not able to produce satisfactory conversions of chloroarenes. Thus, the stronger but more nucleophilic base NaO-*t*-Pent was required for obtaining optimized yields (method C4 *vs.* C2), although significant transesterification occurred.[37] Phenethylamine was coupled accordingly with 30% yield (entry 20).

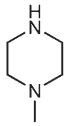
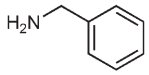
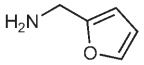
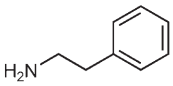
Without a possibility for this transesterification side reaction to take place, yields for the second amination with benzyl derivatives increased from 21–38% within the methyl benzoate subset (entries 18 and 19) to around 55% within the benzonitrile series (entries 21 and 22). In accordance with the experiences made for an attachment of 2-phenoxyethylamine to nitrobenzenes (Table 2, entry 8), said amine was introduced smoothly to a 2-chlorobenzonitrile using $K_3PO_4$ as base in 43% (entry 23).

For electron-rich substrates (Table 5), the first amination with *N*-methylpiperazine succeeded similarly to the respective step on benzonitriles with around 65% yield (method A, *cf.* Table 4, entry 21). Subsequent introduction of benzyl-, furfuryl- and phenethylamine was achieved in excellent yields of 50 to 75% (entries 24–26). As is deducible from the literature,[28] a Xantphos-based protocol for the implementation of carbamates was not suitable for electron-rich bromoarenes (no coupling of *N*-Boc-benzylamine with 1-benzyloxy-2-bromo-4-chlorobenzene detectable, method F1).

**Table 5.** Two-fold amination of 2,4-dihalogenated phenol ethers.




| Entry | X | 1st Amination (at Br site) Amine | Procedure[a] | Yield | 2nd Amination (at Cl site) Amine | Procedure[a] | Yield |
|---|---|---|---|---|---|---|---|
| 24 | OMe/OBn |  | A | 68/61% |  | C2 | 28%[b]/n.a. |
| | | | | | | C4[c] | 75/68% |
| 25 | | | | |  | C4[c] | 58/53% |
| 26 | | | | |  | C4[c] | 73/50% |

[a] **A**: Ar-Br/amine 1.0:1.1; 0.05 equivs. (DPPF)$PdCl_2$, 0.15 equivs. DPPF (**1**), 1.25 equivs. NaO-*t*-Pent, THF (2 mL mmol$^{-1}$ Ar-Br), 100 °C, 4 h; **C2**: Ar-Cl/amine 1.0:1.3; 0.10 equivs. $Pd(OAc)_2$, 0.20 equivs. (biph)P(*t*Bu)$_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (2 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **C4**: Ar-Cl/amine 1.0:1.3; 0.05 equivs. $Pd_2dba_3$, 0.20 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene (2 mL mmol$^{-1}$ Ar-Cl), 110 °C, 20 h; **F1**: Ar-Br/amine 1.0:1.1; 0.03 equivs. $Pd(OAc)_2$, 0.045 equivs. Xantphos (**4**), 1.4 equivs. $Cs_2CO_3$, dioxane (1 mL mmol$^{-1}$ Ar-Br), 110 °C, 20 h.

[b] Incomplete conversion, starting chloroarene detectable.

[c] LC-MS indicated complete conversion, differences in yields due to work-up.

Isolated yields, yields are not optimized; n.a. = not applied.

For transformations which had to be classified as failures, including conversions of certain acetoxy, acetamide and sulfonamide haloarenes, *cf.* Supporting Information.

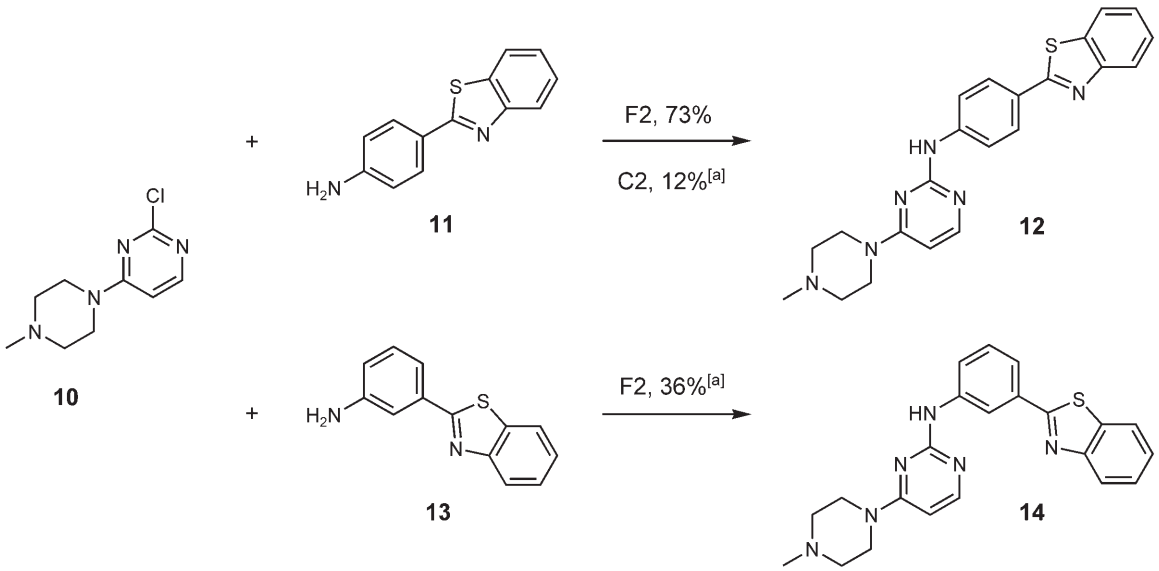
## Amination of Chloropyrimidines and -quinazolines: Xantphos-Based Catalysis

Among kinase inhibitors, aminopyrimidines and -quinazolines belong to the most potent scaffolds.[38] Direct nucleophilic substitution of chlorine in 2-position of the former with anilines – accelerated by HCl formed intermediary – is usually the synthetic mode of choice,[39] but failed for the conversion of 2-chloro-4-(*N*-methylpiperazino)pyrimidine (**10**). Weak nucleophiles in Pd-catalyzed aromatic aminations are generally converted smoothly using Xantphos (**4**) as ligand (*vide supra*),[28–30] which was likewise suitable for amination of chloropyrimidines and -pyridines as substrates,[29] whereas (biph)P(*t*-Bu)$_2$ **3a** or BINAP (**2**) can effectively couple chloropyridines with good N-nucleophiles.[3,14,40] This general notion was confirmed with 2-(4-aminophenyl)-benzothiazole (**11**), a phenylogous 2-aminothiazole and thus weak nucleophile, which was attached to chloropyrimidine **10** in an excellent yield of 73% (method F2, Xantphos), as compared to only 12% of product **12** being isolated when (biph)P(*t*-Bu)$_2$ **3a** was used as ligand (method C2, Scheme 1). The diminution in efficacy when changing to 2-(3-aminophenyl)-benzothiazole (**13**, 36% yield) seemed to be simply a result of increased nucleophilicity of the amine due to the shift of the electron-withdrawing thiazole unit from the *para* to the *meta* position, thus rendering Xantphos (**4**) a sub-optimal ligand.

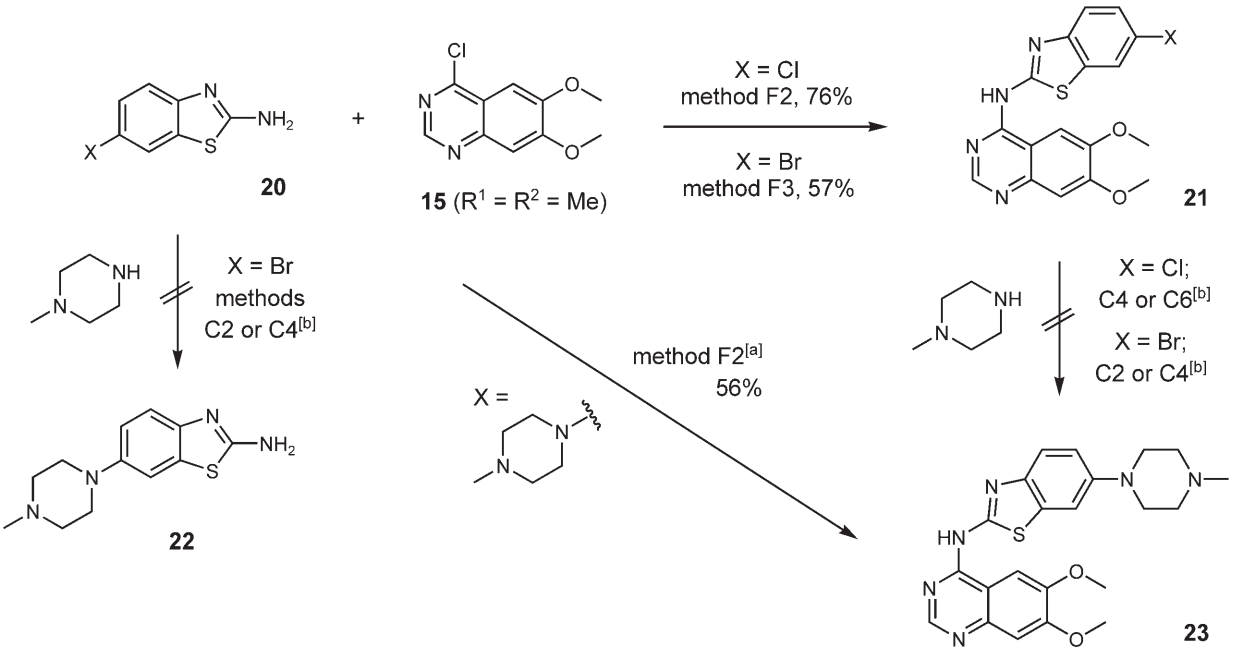
With more complex molecules for which a direct nucleophilic amination failed due to the low nucleophilicity of the amine substrates, a Xantphos-based protocol for palladium-catalyzed amination reactions (method F2) yielded the desired products. Yields as depicted in Table 6, however, should not be used for comparison of efficacy as a fast and simple purification procedure was applied (a rinsing sequence), so that some product loss occurred depending on their solubility. Generally, when 4-chloroquinazolines **15** were aminated using a further functionalized aminobenzothiazole **16**, conversions were quite excellent, isolated yields for **17** ranged from 40 to 81%. A free phenolic hydroxy group did not interfere with the amination process (81% yield, entry 4) and even the corresponding 4-chloro-7-acetoxyquinazoline ($R^1$ = Me, $R^2$ = Ac; not shown) was converted successfully using this procedure.[41] A 2-aminobenzooxazole **18** was likewise introduced with excellent 75% yield.

A good example of complete chemoselectivity is shown in Scheme 2, where aminobenzothiazoles **20** were exclusively attached to the 4-chloroquinazoline




**Scheme 1. C2**: Ar-Cl/amine 1.0:1.2; 0.04 equivs. $Pd_2dba_3$, 0.16 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (2 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **F2**: Ar-Cl/amine 1.0:1.2; 0.04 equivs. $Pd_2dba_3$, 0.12 equivs. Xantphos (**4**), 1.4 equivs. $K_3PO_4$, dioxane (4 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h. [a] Incomplete conversion, starting chloropyrimidine detectable. Isolated yields, yields are not optimized.

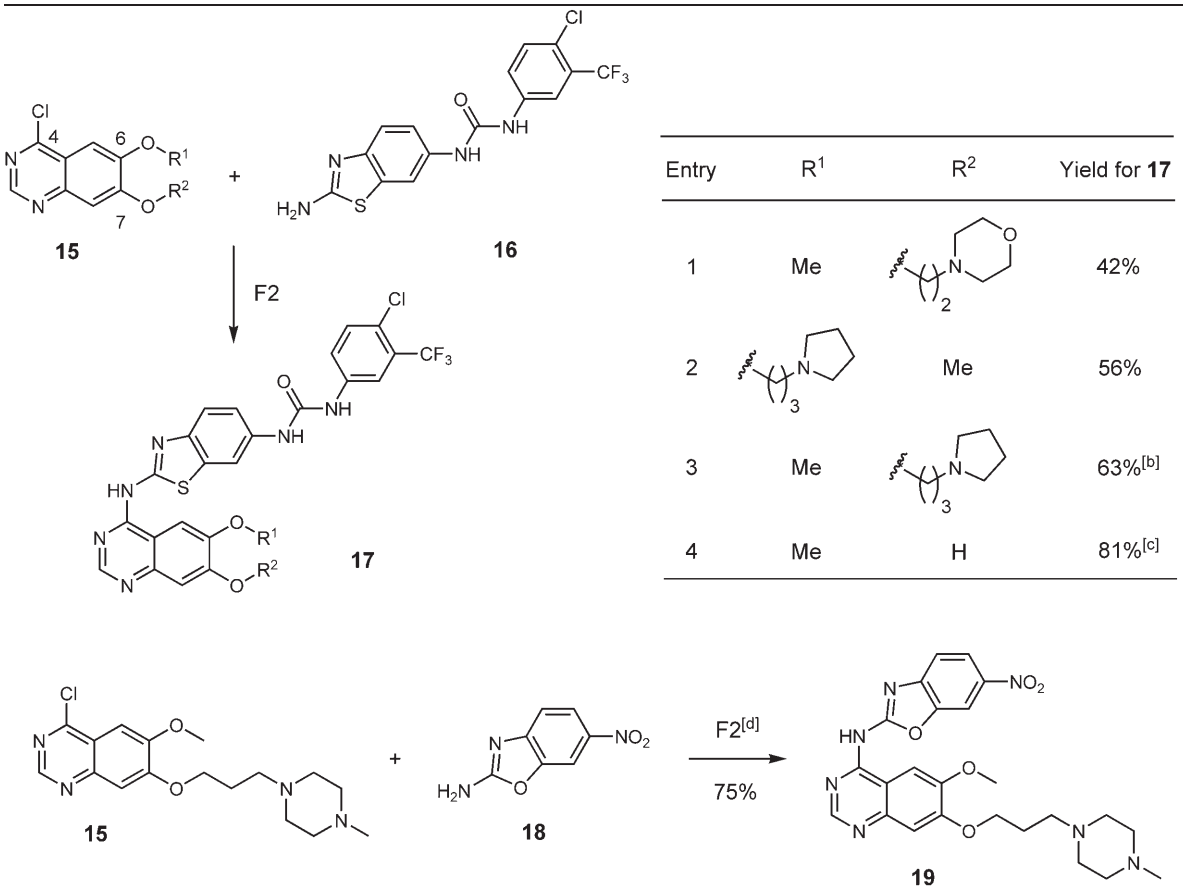



**Scheme 2. C2**: Ar-Br/amine 1.0:1.1; 0.05 equivs. $Pd_2dba_3$, 0.15 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. $K_3PO_4$, DME (10 mL mmol$^{-1}$ Ar-Br), 100 °C, 20 h; **C4**: Ar-Hal/amine 1.0:1.1; 0.05 equivs. $Pd_2dba_3$, 0.15 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene (10 mL mmol$^{-1}$ Ar-Hal), 110 °C, 20 h; **C6**: Ar-Cl/amine 1.0:1.1; 0.1 equivs. $Pd(OAc)_2$, 0.15 equivs. (biph)$PCy_2$ **3b**, 1.4 equivs. NaO-*t*-Pent, toluene (10 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h; **F2**: Ar-Cl/amine 1.0:1.0; 0.02 equivs. $Pd_2dba_3$, 0.06 equivs. Xantphos (**4**), 1.4 equivs. $K_3PO_4$, dioxane (5 mL mmol$^{-1}$ Ar-Cl), 100 °C, 6 h; **F3**: Ar-Cl/amine 1.0:1.0; 0.02 equivs. $Pd_2dba_3$, 0.06 equivs. Xantphos (**4**), 1.4 equivs. $K_3PO_4$, 0.16 equivs. $H_2O$, dioxane (3 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h. [a] Reaction time 20 h. [b] No conversion, only starting haloarene detectable. Isolated yields, yields are not optimized.

**15** despite a bromine or chlorine substituent at the aromatic ring (Xantphos-based protocols F2 and F3). For conversion of **20**, X = Br, addition of water was advantageous (method F3) for achieving high conversions, as was suggested in the literature for certain transformations, most likely caused by higher solubility of the base.[25,29]

**Table 6.** Amination of 4-chloroquinazoline with 2-aminobenzothiazoles and -oxazoles.[a]




| Entry | $R^1$ | $R^2$ | Yield for **17** |
|---|---|---|---|
| 1 | Me |  | 42% |
| 2 |  | Me | 56% |
| 3 | Me |  | 63%[b] |
| 4 | Me | H | 81%[c] |

[a] **F2**: Ar-Cl/amine 1.0:1.0; 0.02 equivs. $Pd_2dba_3$, 0.06 equivs. Xantphos (**4**), 1.4 equivs. $K_3PO_4$, dioxane (10 mL mmol$^{-1}$ Ar-Cl), 100 °C, 20 h.
[b] Conducted with 5 mL dioxane/mmol Ar-Cl.
[c] Conducted with 1.1 equivs. $K_3PO_4$, 5 mL dioxane/mmol Ar-Cl, 100 °C, 6 h.
[d] Conducted with 3 mL dioxane/mmol Ar-Cl.
Isolated yields, yields are not optimized.

Unfortunately, a subsequent replacement of the halogen in **21** by *N*-methylpiperazine failed under various conditions [X = Cl, methods C4 and C6, the latter comprising (biph)$PCy_2$ **3b**, Figure 1; X = Br, methods C2 and C4]. This problem seemed to be intrinsic to the aminobenzothiazole unit and was most likely not caused by other parts of the complex molecule **21** as was shown in a likewise unsuccessful amination of **20** (X = Br) directly with *N*-methylpiperazine (methods C2 and C4), which did not yield compound **22**.[42] With *N*-methylpiperazine being installed differently by a multistep synthesis not involving palladium chemistry, the complete unit **20** (X = *N*-methylpiperazinyl) was finally attached to chloroquinazoline **15** to give **23** with 56% yield (method F2).

## Parallel Amination Chemistry

For another series of compounds, displaying inhibitory effects on certain protease activities, a parallel synthetic approach using Pd-catalyzed amination reactions was established. Using a GreenHouse Parallel Synthesiser™ from Radleys Discovery Technology (RDT), vials were not sealed separately but were heated in a joined argon atmosphere with nickel condensing fingers positioned within every individual glass reaction tube. Some adaptations of standard method C4 had to be performed to allow for an easy charging of all vials with catalyst. For the arylation of a certain piperidine derivative (here **24**) with differently substituted bromoarenes **25** (Table 7), stock solutions of **24** and of $Pd_2dba_3$ and (biph)P(*t*-Bu)$_2$ **3a** were prepared, aliquots of which were pipetted into each reaction vial (method C7). Products **26** were isolated with 10 to 40% yield upon filtration and HPLC

purification, with only 8-bromoquinoline resulting in no significant conversion (entry 7).

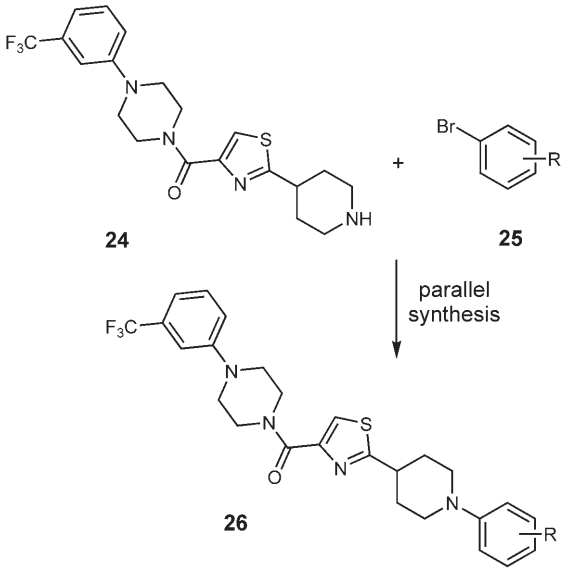
## Conclusions

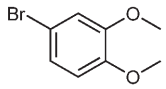
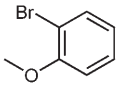
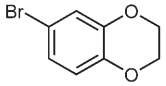
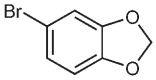
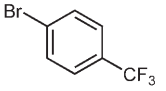
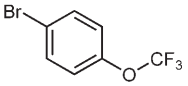
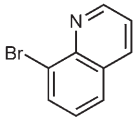
Generally, Pd-catalyzed amination reactions were shown to be successful for a greatly diversified set of substrates, even though a profound fine-tuning of the catalytic system seems unavoidable when mediocre yields are not tolerable. In our case, the major goal was to gain sufficient quantities of product for biological testing and yields obtained were thus acceptable.

As a most versatile and generally applicable procedure, Buchwald's system based on (biph)P(*t*-Bu)$_2$ **3a** as ligand with either NaO-*t*-Pent or $K_3PO_4$ as base was identified: this protocol yielded good results for chloroarenes in combination with secondary alicyclic amines, benzylamines (except with 2-chloronitroarenes[14]), aminopyrroles and 2-substituted ethylamines, and was likewise usable for bromoarene substrates. For a chemoselective first amination of bromochloroarenes, less reactive catalytic systems were chosen which usually were only amenable to aryl bromides. Diversity was best introduced on aryl bromides (thus in a first amination step), which still allow for aminations with a greater variety of amines as compared to aryl chlorides. The appropriate choice of ligand in these cases was crucial for certain subgroups of N-nucleophiles, hence amination reactions could not be performed using a general catalytic system. The most robust system for the arylation of bromoarenes with benzylamines and piperazines was according to Hartwig's DPPF-based procedure. Aminations using BINAP/$Cs_2CO_3$ proved to be an excellent alternative for substrates bearing base sensitive functional groups, N-heterocycles were best arylated by copper catalysis. For substituted carbamates, primary and secondary amides and other weak N-nucleophiles like 2-aminobenzothiazoles and -oxazoles, Xantphos-based protocols were identified to be very versatile and reliable, enabling amination reactions of aryl bromides, chloropyrimidines and chloroquinazolines. However, electron-rich aryl bromides, like *ortho*-alkoxybromoarenes, were found to represent challenging substrates for Xantphos-mediated aminations, only very rare examples of which have been published so far.[28,29,31] In all cases of amination reactions of bromochloroarenes, the chlorine site was never aminated prior to the bromine site.

Arylation of 5-membered N-heterocycles proved to be tricky for substrate combinations chosen here, which were not suitable to assess the general applicability of these procedures. Proceeding still with poor yields but at least yielding some product, copper-based protocols showed to be superior over Pd-catalyzed reactions, though. Generally, 2-bromonitroar-

**Table 7.** Parallel amination reactions using a GreenHouse Parallel Synthesiser™.[a]




| Entry | Bromoarene **25** | Yield for **26** |
|---|---|---|
| 1 |  | 40% |
| 2 |  | 20% |
| 3 |  | 37% |
| 4 |  | 22% |
| 5 |  | 10% |
| 6 |  | 14% |
| 7 |  | traces[b] |

[a] **C7**: stock solution I – amine **24** in toluene/DMA (4:1, 10 mL mmol$^{-1}$ amine); stock solution II – $Pd_2dba_3$, (biph)P(*t*-Bu)$_2$ **3a** (Pd/L = 1:2) in toluene (200 mL mmol$^{-1}$ $Pd_2dba_3$); reaction vial was charged with 1.4 equivs. NaO-*t*-Pent, 1 mL of each stock solution I and II, and 1.0 equivs. of aryl bromide **25** dissolved in 1 mL toluene; final conditions: Ar-Br/amine 1.0:1.0; 0.05 equivs. $Pd_2dba_3$, 0.2 equivs. (biph)P(*t*-Bu)$_2$ **3a**, 1.4 equivs. NaO-*t*-Pent, toluene/DMA (14:1, 30 mL mmol$^{-1}$ Ar-Br), 100 °C, 20 h.

[b] Product traces detected by LC-MS, along with only starting bromoarene.

Isolated yields, yields are not optimized.

enes represented problematic substrates for Cu-catalyzed amination processes, as side reactions were quite competitive, using up the catalytic species. Additionally, combinations of sterically demanding substrates (i.e., *ortho* substituted) were reportedly unsuitable for such Cu-mediated conversions.

For a few substrates like certain acetoxy and sulfonamide substituted bromoarenes, none of the general protocols yielded any product at all. According to the literature, some challenging substrates might be converted successfully by utilizing specialized ligands like **3c** (Figure 1), calling for an elaborated fine-tuning of the catalytic system, which, however, was not aimed at in this work.

Finally, aminations of nitroarenes and methyl benzoates confirmed their potential for decomposition in coupling reactions applying NaO-*t*-Pent as base.[2,3,13,14,16,17] Interestingly, this effect was strongly pronounced for aminations of arylchlorides with (biph)P(*t*-Bu)$_2$ **3a** as ligand and of aryl bromides using BINAP (**2**) – with DPPF (**1**), however, quite decent yields of 25–38% were attained (Tables 1, 2 and 4). Despite this incompatibility with base-sensitive head groups, NaO-*t*-Pent became base of choice for certain amination reactions of such *ortho* substituted aryl chlorides, in which the use of $K_3PO_4$ in combination with ligand **3a** resulted in almost no conversion, or side reactions (e.g., Heck-type coupling) dominated, with the stronger base accelerating the catalytic cycle for amination reactions and thus subduing unwanted reaction channels (Tables 2-4, entries 7, 13, 18, 19).

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.

For a detailed comparison of the scope of transition metal catalyzed aromatic amination and $S_NAr$ protocols, see Supporting Information.

## Experimental Section

### General Remarks

$Pd_2dba_3$, all phosphine and amine ligands were purchased from STREM Chemicals except for *rac*-BINAP (**2**) and (biph)$PCy_2$ (**3b**), which were obtained from Sigma Aldrich and Acros, respectively. $Pd(OAc)_2$ was purchased from Acros, CuI and (DPPF)$PdCl_2$ from Sigma Aldrich. Sodium *tert*-pentylate, $K_3PO_4$, sodium phenolate trihydrate and KOH were ordered from Sigma Aldrich, KOH was finely ground and dried in high vacuum over night prior to use. $Cs_2CO_3$ and $K_2CO_3$ were obtained from Acros. All organic solvents were purchased from Sigma Aldrich as Sure/Seal™, $H_2O$ was de-ionized and degassed prior to use. The following halogenated arenes were commercially available: 1-bromo-4-chloro-2-nitrobenzene (Table 1, entries 1 and 2), 5-bromo-2-chloroanisole (Table 1, entry 4), 4-bromo-2-chlorobenzonitrile (Table 4, entries 21–23), 2-bromo-4-chloroanisole (Table S1, entry 1; Supporting Information), 4-bromo-2-chlorobenzenesulfonamide (Table S1, entry 4). All substrates, reagents and solvents were used without further purification. Yields were not further optimized, no efforts were made to isolate product from all HPLC fractions or mother liquors.

### General Procedure for Transition Metal-Catalyzed Amination Reactions

An oven-dried vial with screw top was charged with all solid or oily reactants: catalyst, ligand (except for amine ligand *rac*-**5**), base, aryl halide, and – if applicable – the respective amine. The tube was evacuated and purged with argon, and solvent and – if applicable – liquid reactants (e.g., *N*-methylpiperazine, amine ligand *rac*-**5**) were added with a syringe or Eppendorf pipette. The vial was sealed (screw cap with septum) and heated for a certain period. Ratios of reactants and substrates as well as temp. and reaction time can be deduced from the Table and Scheme captions within the main text.

Reaction scale ranged from 0.1 to 8.0 mmol aryl halide, most standard reactions of Tables 1 to 5 were conducted at a 0.4 or 0.8 mmol scale, reactions of Scheme 1 and Scheme 2 and Table 6 were started with 0.1–0.3 mmol aryl chloride, parallel reactions of Table 7 were conducted with 0.1 mmol starting material. For upscale reactions, 1.0 to 8.0 mmol aryl halide were used.

### Supporting Information

Work-up and spectral data for all compounds, including side products, are given in the Supporting Information.

## Acknowledgements

*Synthetic support by Dr. A. Wuzik and a skilled preparative HPLC/LC-MS performance by O. Müller were highly appreciated.*

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[2] For review articles, see: a) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2046–2067; b) D. Prim, J.-M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041–2075; c) ref.[3]

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[10] These demands are in clear contrast to those for industrial scale-up, examples of which using Pd-catalyzed amination reactions have been published most recently: elaborate fine-tuning of reaction conditions has to be performed to optimize yields, reduce side reactions, facilitate workup or decrease hazardous potential due to exothermic conversions and to decrease amount of catalyst to get dirt-cheap and thus economically attractive processes; see S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23–39.

[11] Several applications of catalyzed aromatic aminations in industrial research have been reported in the recent past, these – however – rather focused on the introduction of a defined amine into a special target molecule, including a detailed ligand screen and condition optimization, and did not aim at the generation of diverse libraries around one structural core unit. For a review on such applications with a focus on practical issues of the methodology, see B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

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lished for iodoarenes in combination with similar amine substrates; see ref.[7]

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