Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 2938–2950
Tetrahedron
www.elsevier.com/locate/tet

Palladium-catalyzed monoamination of dihalogenated benzenes

Simon Birksø Larsen [b], Benny Bang-Andersen [a], Tommy Nørskov Johansen [b], Morten Jørgensen [a,*]

[a] *Medicinal Chemistry Research, H. Lundbeck A/S, 9 Ottiliavej, DK-2500 Valby, Denmark*
[b] *Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, 2 Universitetsparken, DK- 2100 Copenhagen, Denmark*

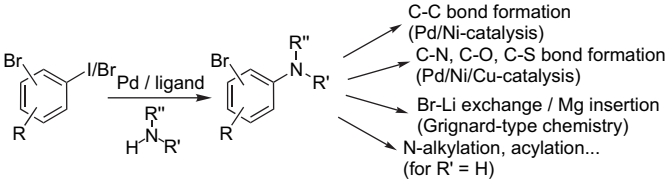
Received 6 November 2007; received in revised form 11 January 2008; accepted 17 January 2008
Available online 25 January 2008

Abstract

The palladium-catalyzed monoamination of symmetric dibromobenzenes can be performed using a catalyst based on Pd_2dba_3 and BINAP in the presence of NaO(*t*-Bu). The analogous transformation of non-symmetric bromoiodobenzenes is most effectively performed with Xantphos as the ligand, while reactions with BINAP were non-selective. These transformations can be scaled uneventfully to >10 g quantities. They do not require drybox or Schlenk techniques, and all reagents are weighed out in air. The resulting monobromoanilines are versatile intermediates for further synthetic transformations.

1. Introduction

Dibromobenzenes and selectively functionalized iodinated aryl bromides are readily prepared by well-established synthetic methods such as diazotization, directed *ortho*-metalation, and bromination/iodination reactions. A selective monoamination of such compounds would provide versatile intermediates for further chemical elaboration as outlined in Scheme 1. The remaining bromide substituent can be utilized in the construction of C–C, C–N, C–O, or C–S bonds via transition metal-catalyzed cross-coupling reactions. Lithium–bromide exchange or Grignard reagent formation can be used as routes to metalated species, which may be used as 'classic' nucleophiles as well as participate in palladium-catalyzed Negishi (after transmetalation to zinc) and Kumada reactions. Finally, secondary anilines lend themselves to more traditional chemical transformations such as alkylation and acylation, and they are easily converted into sulfonamides and ureas.



Scheme 1. Chemical utility of products originating from monoamination of dihalogenated aromatics.

Many medicinal chemistry programs focus on aromatic scaffolds. Palladium-catalyzed cross-coupling reactions are widely used to prepare the desired molecules.[1] Chlorine is often an important substituent in the final molecules, leaving the medicinal chemist with iodides and bromides in addition to nonaflates/triflates as the reactive sites in cross-coupling reactions. In view of the nature of medicinal chemistry, the advantages in terms of speed associated with an easy-to-perform, regioselective reaction of an aryl bromides/iodides would greatly out-weigh the higher price of these compounds compared to, e.g., chlorobenzenes. In our experience, the highly active 'modern' catalysts are often difficult to control when it comes to polyhalogenated arenes, while their less reactive 'classic' counterparts offer better regio- and chemoselectivities.

* Corresponding author. Tel.: +45 36433965; fax: +45 36438303.
E-mail address: mojj@lundbeck.com (M. Jørgensen).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.070

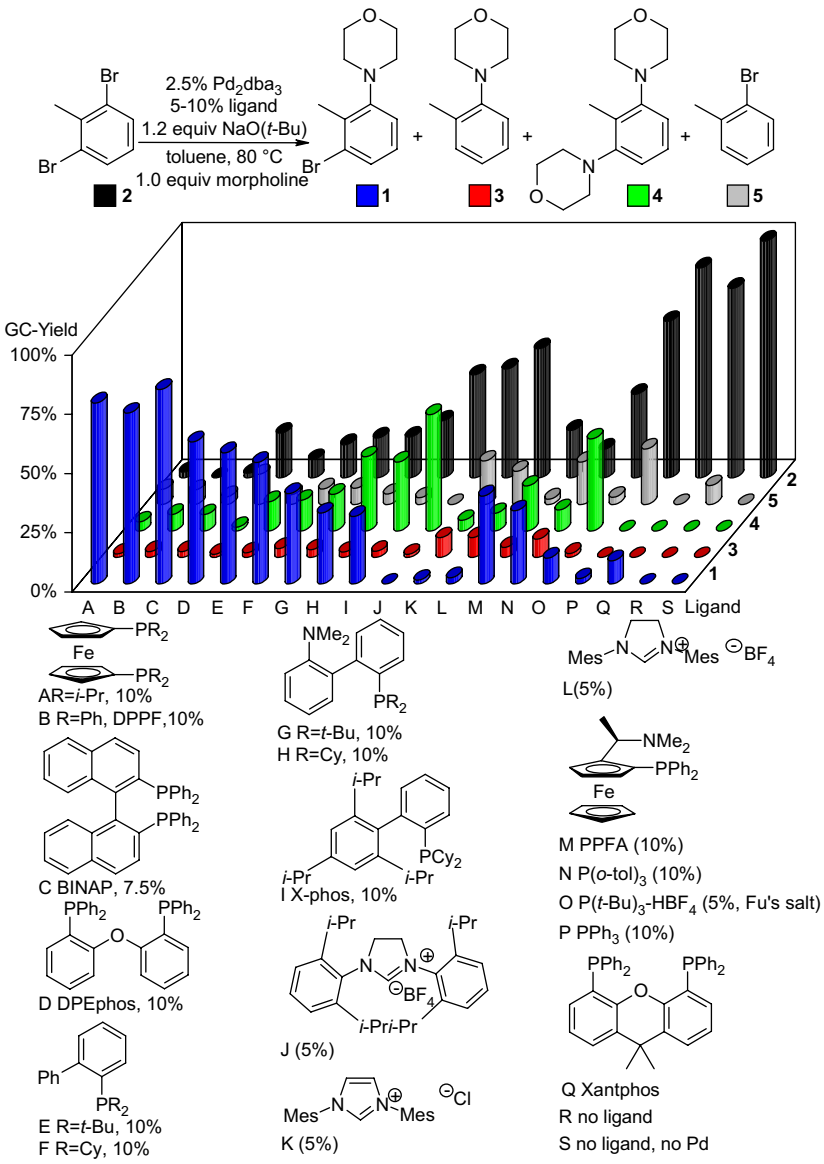


Figure 1. Ligand optimization experiments. Reactions were performed on 1.0 mmol scale using 2.5% Pd_2dba_3 and 5–10% ligand in dry toluene (2.5 mL) in closed vials at 80 °C for 20 h. GC yields were determined using *n*-dodecane as internal standard and are indicated by the colored bars across the range of ligands evaluated (denoted by capital letters).

The Buchwald–Hartwig reaction has revolutionized the synthesis of phenyl piperazines and related privileged structures.[2] This transformation that couples amines to aryl halides in the presence of a palladium or nickel catalyst was first reported in the mid-1980s.[3] Despite the broad substrate scope of the currently available catalyst systems, only few examples of selective monoarylation of dihalogenated benzenes are reported in the literature.[4] The present paper describes solutions to this problem in the form of general protocols for the monoamination of symmetric dibromobenzenes and for the selective aryl iodide amination of non-symmetric bromoiodobenzenes, respectively.

2. Results and discussion

An in-house medicinal chemistry project required access to multigram quantities of 4-(3-bromo-2-methylphenyl)-morpholine (**1**). It was decided to test the monoamination of commercially available 2,6-dibromotoluene (**2**) to arrive at the desired molecule in a single step. Based on our experience with the palladium-catalyzed aryl amination reaction, it was anticipated that the choice of a ligand for the palladium catalyst would be a non-trivial matter. Despite the significant advances in aryl amination chemistry, it is fair to state that matching the palladium with a ligand suited for the reaction remains largely a matter of trial and error experimentation.[5]

A selection of commercially available, air-stable catalyst precursors was studied for the reaction with no attempts to exclude air from the reactions (cf. Fig. 1).[6] This approach was associated with the risk that several 'good' catalysts might potentially escape our attention. It was decided that this disadvantage would be more than out-weighed by the identification of a robust catalyst system.

Good to high yields of the desired monoamination product **1** was observed in reactions involving ferrocene ligands,[7] BINAP,[8] DPEphos,[9] and the two 'original' Buchwald ligands.[10] On the other hand, Davephos,[10] X-phos,[10] PPFA,[11] and P(*o*-tol)$_3$ mediated non-selective reactions with significant amounts of hydrodehalogenation products **3** and **5** and/or bisamination product **4**. The carbene ligands[12] gave complex mixtures except for the di-*iso*-propyl ligand (J in Fig. 1) used by Hartwig for the amination of chloroarenes,[13] which in this case gave almost quantitative yield of the diamination product **4**. P(*t*-Bu)$_3$, used as Fu's salt,[14] was non-selective and failed to promote full conversion of the substrate. Very low conversion of **2** was observed with Xantphos as the ligand,[15] an important finding for the selective monoamination of non-symmetric bromoiodobenzenes. No significant conversion of **2** was observed in the absence of palladium and/or ligand. In a similar manner, Xantphos was identified as a suitable ligand from the same set of catalyst precursors for the monoamination of bromoiodobenzenes.

Comparative studies with DPPF, BINAP, and DPEphos for the coupling of 1,2-dibromobenzene and morpholine led to the conclusion that BINAP was the ligand of choice for the desired monoamination of symmetric dibromobenzenes, although DPPF could be used as well (cf. Table 1, entry 1). With BINAP as the ligand, the reaction occurred with comparable yields with Pd_2dba_3, $Pddba_2$, and even $PdCl_2$, while a slightly lower yield was obtained with $Pd(OAc)_2$. $Pd(DPPF)Cl_2/CH_2Cl_2$ was a much less efficient catalyst.

Table 1 summarizes reactions of dibromobenzenes with nitrogen coupling partners. Good yields were obtained with primary aliphatic amines as well as with cyclic secondary aliphatic amines. The substrate scope also included sterically and electronically diverse anilines. The commercially available ammonia equivalents allyl amine[16] and benzophenone imine[17] as well as benzylamine could be used in the reaction with dibromobenzenes. The presence of *ortho*-substituents did not reduce the yield of the reaction. In line with the literature,[10] lower yields were obtained with acyclic, secondary aliphatic amines.

As stated in the introduction, this protocol was developed as a part of a medicinal chemistry project. Gratifyingly, the reaction was directly scaleable to multigram scale to produce the building blocks required toward this end (Table 1, entries 1, 8, 12, and 13). These were used for the preparation of **Lu 37-211** and related compounds, which are dual D_4 receptor antagonists and serotonin reuptake inhibitors and as such potential antipsychotics. Previously, the **Lu 37-211** series had been prepared via the iron-assisted Pearson reaction on solid phase.[18] While this was a powerful tool to prepare small amounts of product in a combinatorial setting, it was very tedious on larger scale. Conversely, the current method enabled the expedient preparation of gram quantities of the lead compounds as exemplified in Scheme 2. This procedure was generally applicable and was used to prepare more than thirty new analogues of **Lu 37-211**. The pharmacological profiles of these compounds will be reported in due course.

It was not possible to achieve the regioselective monoamination of non-symmetric dibromobenzenes with BINAP as the ligand. To overcome this regioselectivity issue, we turned our attention to the higher reactivity of aryl iodides relative to aryl bromides to rely on bromoiodobenzenes as starting materials for the synthesis of non-symmetric bromoanilines. In these cases, BINAP was a suboptimal ligand, while good results were obtained with Xantphos (cf. Table 2).[19] The reaction occurred with exquisite selectivity for the iodide and, as expected, the reaction times were generally much shorter than for the aryl bromides. Equally good results were obtained with aliphatic amines as with anilines. One of the prepared compounds (Table 2, entry 2) has been used previously in the synthesis of the antibacterial agent linezolid, where the intermediate was prepared from 1,2-difluoro-4-nitrobenzene via a classic S_NAr-reaction with morpholine followed by reduction and diazotization.[20]

No attempts were made to minimize the catalyst loadings during this work. The relatively high loading of 5% palladium was chosen to ensure expedient production of the target molecules and does as such represent a 'typical' medicinal chemistry approach in which the timely isolation of the product is more important that the cost of the employed reagents. However, the example in Table 2, entry 5 demonstrates that, at least for aryl iodides, the palladium loading can be reduced to 1% with comparable yield at the expense of a longer reaction time.

3. Conclusion

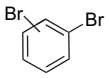
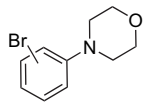
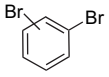
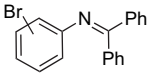
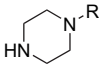
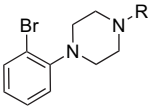
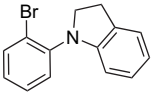
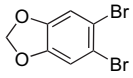
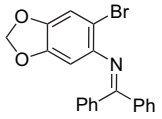
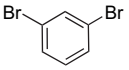
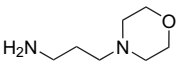
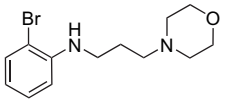
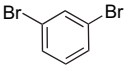
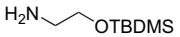
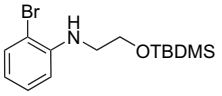
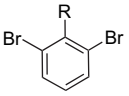
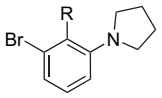
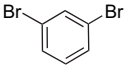
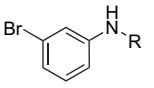
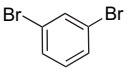
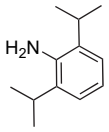
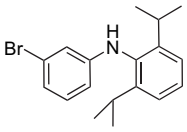
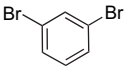
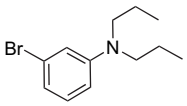
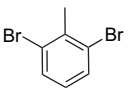
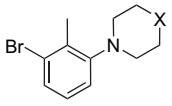
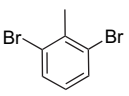
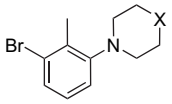
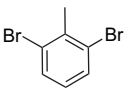
In summary, we have developed procedures for the selective monoamination of symmetric dibromobenzenes and of non-symmetric bromoiodobenzenes using catalysts based on Pd/BINAP and Pd/Xantphos, respectively. The procedure can be scaled up to >10 g with comparable yields.

4. Experimental

4.1. General

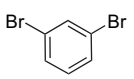
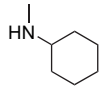
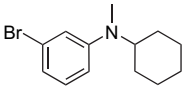
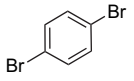
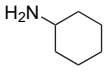
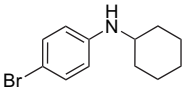
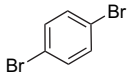
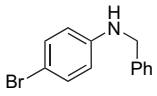
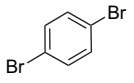
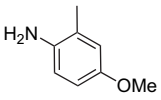
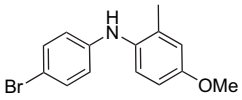
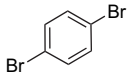
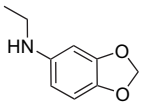
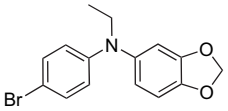
Thin layer chromatography (TLC) was conducted on Merck, Silica gel 60 F_{254}, and visualized by exposure to UV light or appropriate staining reagents. TLC R_f-values refer to the eluent used in column chromatography. Melting points (open capillary method) were taken using a Büchi Melting Point B-540 (Büchi, Switzerland) and are uncorrected. Flash chromatography was performed using Merck Silica Gel 60 (40–63 μm). ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker Avanche AV-500 at 500 MHz and 125 MHz, respectively. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (TMS) or residual solvent, and coupling constants (J) are given in hertz. GC/FID analyses were performed on a Shimadzu GC-2010 equipped with AOC-20i auto injector and AOC-20s auto sampler; column: Supelco Equity-1 fused silica capillary column (30 m×0.25 mm, 0.25 μm film). Unless otherwise noted, starting materials obtained from commercial suppliers were used as received. All new compounds (and previously reported, but unsatisfactorily described compounds) have been fully characterized, including combustion elemental analysis data and/or HRMS data. Elemental analyses were performed by Dr. Johannes Theiner (Mikroanalytisches Laboratorium, Universität Wien, Austria). HRMS were recorded by

Table 1
Monoamination of dibromobenzenes

Entry	Bromoiodobenzene	Amine/imine	Product	Time (h)	Isolated yield (%)
1				2-Br: 7–16 7 3-Br: 16 4-Br: 16	73, 75,[a] 67[b] 72,[c] 48,[d] 73,[e] 67[f] 64 70, 74[a]
2				2-Br: 20 3-Br: 20 4-Br: 20	80 72 71
3				R=Boc: 24 R=Bn: 20	68 72
4				24	84
5				19	66
6				8	68
7				8	58
8				R=H: 4.5 R=Me: 2.5	73, 78[g] 68[a]
9				R=*i*-Pr: 4 R=*t*-Bu: 23 R=allyl: 5	67 51 49
10				5	86
11				20	51
12				X=O: 16 X=CH_2: 3.5	83, 81[a] 84[a]
13				X=NBoc: 3 X=S: 16	82[a] 83[a]
14				5	76[a]

(*continued on next page*)

Table 1 (*continued*)

Entry	Bromoiodobenzene	Amine/imine	Product	Time (h)	Isolated yield (%)
15				20	38
16				3	86
17				4	71
18				14	76
19				16	71

Reactions were performed on 2.0–3.0 mmol scale using 2.5% Pd_2dba_3 and 7.5% BINAP in toluene (2.5 mL/mmol) in closed vials at 80 °C (reaction times and catalyst loading have not been optimized).

[a] >10 mmol scale.

[b] 10% DPPF instead of BINAP.

[c] 5% $Pddba_2$ and 7.5% BINAP.

[d] 5% $Pd(DPPF)Cl_2/CH_2Cl_2$.

[e] 5% $PdCl_2$ and 7.5% BINAP.

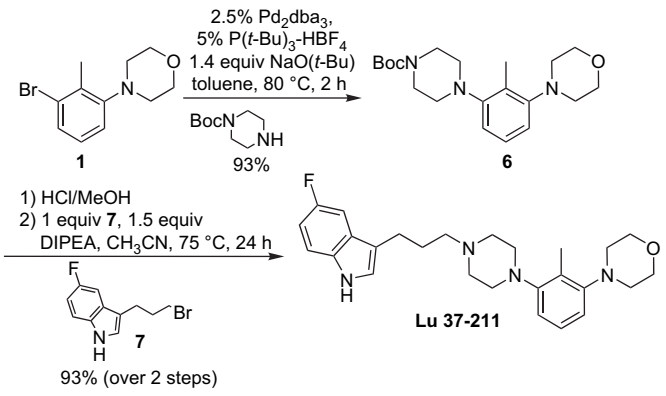
[f] 5% $Pd(OAc)_2$ and 7.5% BINAP.

[g] 1.2 equiv amine.

Dr. Henrik Pedersen and Dr. Jens Christian Madsen (Medicinal Chemistry Research, H. Lundbeck A/S) on a micrOTOF (Bruker Daltonics), operating in the positive ion mode using electrospray ionization (ESI) or APPI. All compounds prepared were judged to be >95% pure by ^{1}H NMR spectroscopy and were homogeneous by TLC.

*4.1.1. 1-(3-Bromo-2-methylphenyl)morpholine (**1**; Table 1, entry 12)*

Starting from 2,6-dibromotoluene (**2**) (500 mg, 2 mmol) and morpholine (174 mg, 2 mmol), general procedure A (16 h) afforded the title compound as a yellow oil (426 mg, 83%). R_f=0.34 (heptane/EtOAc 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, 1H, J=7.9, 1.2 Hz), 7.03 (dd, 1H, J=8.0, 7.9 Hz), 6.98 (dd, 1H, J=8.0, 1.2 Hz), 3.87–3.82 (m, 4H), 2.90–2.86 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 133.0, 127.8, 127.5, 126.7, 118.2, 67.4 (2C), 52.7 (2C), 18.4. HRMS (ESI): *m/z* calcd for $C_{11}H_{15}BrNO$ (MH^+) 256.0332, found 256.0331.



Scheme 2. Synthesis of **Lu 37-211**.

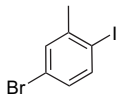
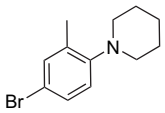
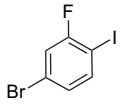
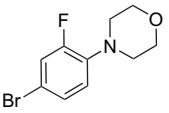
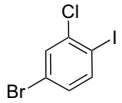
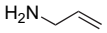
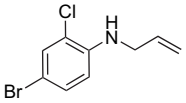
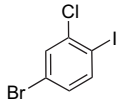
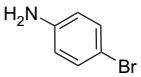
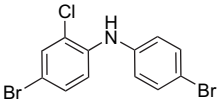
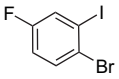
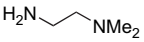
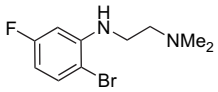
4.1.2. 3-Bromo-2-methylaniline

A reaction flask equipped with a condenser was charged with 1-bromo-2-methyl-3-nitrobenzene (106.8 g, 0.49 mol), activated carbon (10.9 g), $FeCl_3\cdot 6H_2O$ (800 mg, 3 mmol, 0.6% Fe), MeOH (250 mL), and a stir bar. The mixture was refluxed for 10 min. Then $H_2NNH_2\cdot H_2O$ (37.2 mL, 0.77 mol, 1.55 equiv) was added drop-wise over 1.5 h. After refluxing for 7 h, the reaction mixture was allowed to cool to rt before filtering through a pad of Celite. The colorless filtrate was concentrated in vacuo, and the resulting residue was redissolved in EtOAc, dried ($MgSO_4$), and filtered. Concentration in vacuo afforded the title compound as a pale yellow oil (91.6 g, quant.). R_f=0.47 (heptane/EtOAc 7:3). ^{1}H NMR (500 MHz, $CDCl_3$) in agreement with the literature.[21] ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 127.7, 126.0, 122.9, 122.0, 114.2, 17.0.

*4.1.3. 2,6-Dibromotoluene (**2**)*

This compound is commercially available, but since it is rather expensive we have developed the following scaleable

Table 2
Monoamination of bromoiodobenzenes

Entry	Bromoiodobenzene	Amine	Product	Time (h)	Isolated yield (%)
1				2.5	72
2				1	88
3				0.5	90
4				0.5	96[a]
5				40	83[a,b]

Reactions were performed on 2.0 mmol scale using 2.5% Pd_2dba_3 and 10% Xantphos in toluene (2.5 mL/mmol) in closed vials at 80 °C (reaction times and catalyst loading have not been optimized).

[a] 1.2 equiv amine.

[b] Reaction performed on 40 mmol scale with 0.5% Pd_2dba_3 and 2.0% Xantphos.

route. The Sandmeyer catalyst (CuBr) was prepared according to Hartwell.[22] $CuSO_4 \cdot 5H_2O$ (249.7 g, 1.0 mol), NaBr (144.1 g, 1.4 mol, 1.4 equiv), and H_2O (1 L) was placed in a 2-L conical flask. The mixture was gently heated while stirring to get a dark green solution. Na_2SO_3 (63.0 g, 0.5 mol, 0.5 equiv) was added in small portions over a 10-min period. The resulting white suspension was stirred for 10 min before cooling to rt. The suspension was filtered through a Büchner funnel, and the white filter cake was washed with H_2O (2×50 mL). The filter cake was dried overnight in vacuo at 60 °C to afford CuBr as a gray-white solid (136.9 g, 95%). 3-Bromo-2-methylaniline (25.0 g, 0.13 mol) was placed in a three-necked flask equipped with thermometer and stir bar. 48% HBr (40 mL, 2.6 equiv) was added and the resulting pink suspension was briefly heated to 60 °C. After cooling to 0 °C on an ice-water bath, $NaNO_2$ (9.27 g, 0.13 mol, 1.0 equiv) in H_2O (17 mL) was added drop-wise keeping the internal temperature <5 °C by the addition of small pieces of ice. The resulting yellow suspension was stirred, while CuBr (10.6 g, 74 mmol, 0.55 equiv) was weighed into a three-necked flask followed by 48% HBr (9.1 mL, 0.6 equiv). The latter mixture was gently refluxed as the diazonium salt suspension was continuously added from a dropping funnel. After complete addition of the diazonium salt suspension, gentle reflux was continued for 1 h before cooling to rt. The reaction mixture was extracted with 1,2-dichloroethane (3×100 mL) and the combined organic extracts were filtered to remove a white precipitate before concentrating in vacuo. The residue was purified by chromatography (heptane) to afford the title compound as a colorless oil (20.9 g, 62%). R_f=0.74. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[23]

4.1.4. N-(2-Methylphenyl)morpholine (3)

This compound was prepared according to Hartwig et al.[14b] with the following modifications: a vial was charged with $Pd(OAc)_2$ (9.0 mg, 2 mol % Pd), P(*t*-Bu)$_3 \cdot HBF_4$ (Fu's salt[14c]) (9.3 mg, 1.6 mol %), NaO(*t*-Bu) (231 mg, 1.2 equiv), 2-bromotoluene (342 mg, 2 mmol), morpholine (174 mg, 2 mmol), toluene (5 mL), and stir bar. The vial was sealed with a crimp cap and stirred at rt for 24 h. The viscous reaction mixture was taken up in Et_2O (30 mL) and filtered through a pad of Celite. The filtrate was concentrated on 1–2 g of silica. Column chromatography (heptane/EtOAc 6:1) yielded the title compound as a colorless oil (299 mg, 85%). R_f=0.42. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[14b]

4.1.5. 4,4′-(2-Methyl-1,3-phenylene)dimorpholine (4)

A vial was charged with Pd_2dba_3 (34 mg, 5 mol % Pd), BINAP (70 mg, 7.5 mol %), NaO(*t*-Bu) (404 mg, 4.2 mmol, 2.8 equiv), 2,6-dibromotoluene (**2**) (375 mg, 1.5 mmol), morpholine (314 mg, 3.6 mmol, 2.4 equiv), toluene (5 mL), and stir bar. The vial was sealed with a crimp cap and placed in a preheated heating block (100 °C) for 17 h. The reaction mixture was diluted with Et_2O (30 mL) and filtered through a pad of Celite. Concentration on 1–2 g of silica followed by column chromatography (heptane/EtOAc 6:1) afforded the title

compound as an off-white solid (267 mg, 68%). An analytically pure sample was obtained by recrystallization as a white powder, mp 134.9–135.9 °C (MeOH). R_f=0.17. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, 1H, J=8.0 Hz), 6.80 (d, 2H, J=8.0 Hz), 3.89–3.82 (m, 8H), 2.95–2.89 (m, 8H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8 (2C), 127.0, 126.8, 114.1 (2C), 67.6 (4C), 52.4 (4C), 13.4. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.76; H, 8.41; N, 10.53.

4.2. Ligand screening experiments

In air, a 4-mL vial was charged with Pd_2dba_3 (22.9 mg, 5 mol % Pd), ligand, NaO(*t*-Bu) (115 mg, 1.2 mmol, 1.2 equiv), and 2.5 mL of a stock solution (2,6-dibromotoluene (**2**) (0.400 M), morpholine (0.400 M), and *n*-dodecane (0.100 M) in toluene). A stir bar was added before sealing the vial with a screw cap. All vials were simultaneously placed in a preheated aluminum block thermostat (80 °C) and left to stir for 20 h. The vials were removed from the heating block and allowed to cool to rt. Samples for GC/FID analysis were prepared in the following manner: 400 μL of crude reaction mixture was transferred to pentane (400 μL) to precipitate inorganic materials. This mixture was filtered (0.45 μm membrane filter) and 500 μL filtrate was transferred to 1500 μL EtOAc. The latter solution was diluted further (100 μL to 750 μL of EtOAc) before GC injection.

4.3. General procedure A

In air, a vial was charged with reagents: Pd_2dba_3 (46 mg, 5 mol % Pd), BINAP (93 mg, 7.5 mol %), NaO(*t*-Bu) (231 mg, 2.4 mmol, 1.2 equiv), aryl halide (2.0 mmol), and amine or imine (2.0 mmol, 1.0 equiv). Toluene (5 mL) and stir bar were added before sealing the vial and placing it in a preheated aluminum block thermostat (80 °C; an oil bath can be used as well, but the 'alu-block' was preferred because it eliminated the 'mess' of handling a classic oil bath). For larger scale (i.e., >2 mmol), reactions were conducted in reaction flasks connected to a Schlenk line providing a positive pressure of N_2 (at the outset, head space was flushed, but no solvent degassing or other measures were undertaken).

4.3.1. 4-(2-Bromophenyl)morpholine (Table 1, entry 1)

Starting from 1,2-dibromobenzene (472 mg, 2 mmol) and morpholine (174 mg, 2 mmol), general procedure A (16 h) afforded the title compound as a slightly yellow oil (355 mg, 73%). R_f=0.33 (heptane/EtOAc 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[24] Using other ligands or palladium-sources, the following results were obtained: Substituting DPPF (111 mg, 10 mol %) for BINAP in general procedure A (16 h), the title compound was obtained as a pale yellow oil (324 mg, 67%). Substituting $Pd(dba)_2$ (58 mg, 5 mol % Pd) for Pd_2dba_3 in general procedure A (7 h), the title compound was obtained as a pale yellow oil (347 mg, 72%). Using $Pd(OAc)_2$ (23 mg, 5 mol % Pd) instead of Pd_2dba_3 in general procedure A (7 h), the title compound was obtained as a pale yellow oil (325 mg, 67%). Using $PdCl_2$ (18 mg, 5 mol % Pd) in general procedure A (7 h), the title compound was obtained as a pale yellow oil (352 mg, 73%). Using [$PdDPPFCl_2$/DCM] (82 mg, 5 mol % Pd) for Pd_2dba_3 in general procedure A (7 h) gave the title compound as a pale yellow oil (235 mg, 48%).

4.3.2. 4-(3-Bromophenyl)morpholine (Table 1, entry 1)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and morpholine (174 mg, 2 mmol), general procedure A (16 h) afforded the title compound as a pale yellow oil (312 mg, 64%). R_f=0.27 (heptane/EtOAc 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, 1H, J=8.2, 8.0 Hz), 7.02 (dd, 1H, J=2.3, 1.9 Hz), 6.98 (ddd, 1H, J=7.8, 1.7, 0.8 Hz), 6.82 (ddd, 1H, J=8.3, 2.4, 0.8 Hz), 3.84 (t, 4H, J=4.7 Hz), 3.14 (t, 4H, J=4.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 130.5, 123.4, 122.8, 118.6, 114.2, 66.9 (2C), 49.0 (2C). NMR in agreement with reported[25] data run at lower spectrometer frequency.

4.3.3. 4-(4-Bromophenyl)morpholine (Table 1, entry 1)

Starting from 1,4-dibromobenzene (472 mg, 2 mmol) and morpholine (174 mg, 2 mmol), general procedure A (16 h) afforded the title compound as off-white crystals (339 mg, 70%). R_f=0.20 (heptane/EtOAc 6:1). A small amount of material was recrystallized from MeOH to afford a bright-white powder, mp 114.2–115.0 °C (lit.[26] mp 112–113 °C). ^{1}H NMR (500 MHz, $CDCl_3$) in agreement with the literature.[27] ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 131.9 (2C), 117.3 (2C), 112.2, 66.8 (2C), 49.2 (2C).

4.3.4. 2-Bromo-N-(diphenylmethylene)aniline (Table 1, entry 2)

Starting from 1,2-dibromobenzene (472 mg, 2 mmol) and benzophenone imine (363 mg, 2 mmol), general procedure A (20 h) afforded the title compound as an oil, solidifying on standing to afford the title compound as yellow crystals (537 mg, 80%). R_f=0.62 (toluene). A small amount of material was recrystallized from MeOH to afford bright-yellow rod-shaped crystals, mp 105.0–105.5 °C (lit.[28] mp 103–105 °C). ^{1}H NMR (500 MHz, $CDCl_3$) in agreement with the literature.[28] ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 150.3, 138.9, 136.2, 132.5, 131.2, 129.7 (2C), 129.0, 128.8 (2C), 128.4 (2C), 128.0 (2C), 127.6, 124.3, 121.3, 115.4. ^{13}C NMR not in agreement with the literature[28] reporting only 14 carbon signals.

4.3.5. 3-Bromo-N-(diphenylmethylene)aniline (Table 1, entry 2)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and benzophenone imine (363 mg, 2 mmol), general procedure A (20 h) afforded the title compound as a yellow solid (481 mg, 72%). R_f=0.64 (toluene). An analytically pure sample was obtained by recrystallization as yellow needle-shaped crystals, mp 67.6–68.8 °C (MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69–7.61 (m, 2H), 7.55 (tt, 1H, J=7.4, 1.3 Hz), 7.50–7.44 (m, 2H), 7.39–7.31 (m, 3H), 7.20–7.13 (m, 2H), 7.12–7.03 (m, 2H), 6.90 (dd, 1H, J=1.9, 1.8 Hz), 6.71 (ddd, 1H, J=7.6, 1.9, 1.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.6, 152.8, 138.3, 135.4, 131.3, 130.4, 128.9 (2C), 128.8, 128.7 (2C), 128.4 (2C), 128.1 (2C),

125.6, 122.9, 121.3, 119.6. Anal. Calcd for $C_{19}H_{14}BrN$: C, 67.87; H, 4.20; N, 4.17. Found: C, 67.70; H, 4.18; N, 4.08.

4.3.6. 4-Bromo-N-(diphenylmethylene)aniline (Table 1, entry 2)

Starting from 1,4-dibromobenzene (472 mg, 2 mmol) and benzophenone imine (363 mg, 2 mmol), general procedure A (20 h) afforded the title compound as a yellow, highly viscous oil (477 mg, 71%). R_f=0.58 (toluene). A small amount of material was dissolved in MeOH, the solution becoming turbid with the addition of a drop of water. The supernatant was removed, and the residue was concentrated in vacuo to afford a fine yellow powder, mp 81.3–83.0 °C (lit.[29] mp 82–83 °C). ^{1}H NMR (500 MHz, $CDCl_3$) in agreement with the literature.[29] ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 150.4, 139.5, 136.0, 131.6 (2C), 131.1, 129.6 (2C), 129.5 (2C), 129.0, 128.4 (2C), 128.2 (2C), 122.9 (2C), 116.4. ^{13}C NMR not in agreement with the literature[29] reporting 13 carbon signals including one at 103.6 ppm.

4.3.7. tert-Butyl 4-(2-bromophenyl)piperazine-1-carboxylate (Table 1, entry 3)

Starting from 1,2-dibromobenzene (472 mg, 2 mmol) and *tert*-butyl piperazine-1-carboxylate (373 mg, 2 mmol), general procedure A (24 h) afforded the title compound as a slightly yellow, highly viscous oil (464 mg, 68%). R_f=0.49 (heptane/Et_2O 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (ddd, 1H, J=8.0, 7.4, 1.5 Hz), 7.27 (dd, 1H, J=7.9, 1.5 Hz), 7.02 (dd, 1H, J=8.0, 1.5 Hz), 6.93 (ddd, 1H, J=7.9, 7.4, 1.5 Hz), 3.61 (t, 4H, J=4.7 Hz), 2.98 (t, 4H, J=4.6 Hz), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 150.6, 134.0, 128.5, 124.8, 121.2, 120.2, 79.9, 51.8 (2C), 44.5 (br s, 2C, rotamer), 28.6 (3C). HRMS (ESI): *m/z* calcd for $C_{15}H_{22}BrN_2O_2$ (MH^+) 341.0859, found 341.0855.

4.3.8. 1-Benzyl-4-(2-bromophenyl)piperazine (Table 1, entry 3)

Starting from 1,2-dibromobenzene (472 mg, 2 mmol) and 1-benzylpiperazine (353 mg, 2 mmol), general procedure A (20 h) afforded the title compound as a viscous, slightly orange oil (479 mg, 72%). R_f=0.30 (heptane/Et_2O 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, 1H, J=7.9, 1.5 Hz), 7.39–7.30 (m, 4H), 7.29–7.22 (m, 2H), 7.05 (dd, 1H, J=8.0, 1.5 Hz), 6.90 (ddd, 1H, J=7.8, 7.4, 1.5 Hz), 3.59 (s, 2H), 3.07 (br s, 4H), 2.65 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 138.3, 134.0, 129.4 (2C), 128.4 (2C), 128.4 (1C), 127.2, 124.4, 121.1, 120.0, 63.3, 53.5 (2C), 51.8 (2C). HRMS (ESI): *m/z* calcd for $C_{17}H_{20}BrN_2$ (MH^+) 331.0804, found 331.0815.

4.3.9. 1-(2-Bromophenyl)indoline (Table 1, entry 4)

Starting from 1,2-dibromobenzene (708 mg, 3 mmol) and indoline (358 mg, 3 mmol), general procedure A (24 h) afforded the title compound as a colorless, viscous oil (694 mg, 84%). R_f=0.88 (pentane/(i-Pr)$_2$O 10:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (dd, 1H, J=8.0, 1.3 Hz), 7.51–7.39 (m, 2H), 7.24–7.12 (m, 2H), 6.96 (ddd, 1H, J=7.9, 7.9, 1.1 Hz), 6.69 (ddd, 1H, J=7.4, 7.4, 1.0 Hz), 6.23 (d, 1H, J=7.8 Hz), 3.84 (br s, 2H), 3.10 (t, 2H, J=8.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.1, 143.7, 133.8, 130.0, 129.2, 127.4, 126.8, 126.0, 124.8, 121.3, 118.6, 108.6, 53.9, 28.3. HRMS (ESI): *m/z* calcd for $C_{14}H_{13}BrN$ (MH^+) 274.0226, found 274.0216.

4.3.10. 6-Bromo-3,4-methylenedioxy-N-(diphenylmethylene)-aniline (Table 1, entry 5)

Starting from 1,2-dibromo-4,5-methylenedioxybenzene (560 mg, 2 mmol) and benzophenone imine (363 mg, 2 mmol), general procedure A (19 h) afforded the title compound as an oil, affording yellow crystals on standing (504 mg, 66%). R_f=0.29 (heptane/TBME 10:1). An analytically pure sample was obtained by recrystallization as a bright-yellow powder, mp 98.7–99.9 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.75 (m, 2H), 7.48 (tt, 1H, J=7.4, 1.3 Hz), 7.44–7.37 (m, 2H), 7.35–7.27 (m, 3H), 7.21–7.15 (m, 2H), 6.92 (s, 1H), 6.09 (s, 1H), 5.85 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 147.3, 144.4, 144.2, 139.0, 136.3, 131.2, 129.6 (2C), 129.1, 128.8 (2C), 128.4 (2C), 128.2 (2C), 112.1, 105.6, 102.5, 101.6. Anal. Calcd for $C_{20}H_{14}BrNO_2$: C, 63.18; H, 3.71; N, 3.68. Found: C, 63.10; H, 3.66; N, 3.69.

4.3.11. 3-Bromo-N-(3-morpholino-n-propyl)aniline (Table 1, entry 6)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and 3-morpholinopropylamine (288 mg, 2 mmol), general procedure A (8 h) afforded the title compound as a slightly orange, viscous oil (408 mg, 68%). R_f=0.50 (EtOAc/Et_3N 8:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, 1H, J=8.0, 8.0 Hz), 6.78 (dd, 1H, J=7.9, 1.5 Hz), 6.74–6.69 (m, 1H), 6.49 (dd, 1H, J=8.1, 1.5 Hz), 4.80 (br s, 1H), 3.74 (t, 4H, J=4.6 Hz), 3.17 (td, 2H, J=6.6, 4.6 Hz), 2.56–2.30 (m, 6H), 1.78 (tt, 2H, J=6.5, 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 130.6, 123.5, 119.8, 115.0, 111.6, 67.2 (2C), 57.7, 53.9 (2C), 43.3, 25.3. HRMS (ESI): *m/z* calcd for $C_{13}H_{20}BrN_2O$ (MH^+) 299.0754, found 299.0755.

4.3.12. 2-(tert-Butyldimethylsilyloxy)ethanamine (Table 1, entry 7)

A 500-mL, flame-dried, three-necked flask was charged with DMAP (916 mg, 8 mmol, 0.1 equiv), TBDMSCl (12.41 g, 83 mmol, 1.1 equiv), ethanolamine (4.58 g, 75 mmol), 1,2-dichloroethane (150 mL), and a stir bar. The flask was sealed with septa and evacuated/backfilled with N_2 three times before adding Et_3N (15.6 mL, 113 mmol, 1.5 equiv) while stirring. The white, turbid reaction mixture immediately became more viscous. After stirring for 6 h, the reaction mixture was quenched with MeOH (50 mL). The resulting transparent and colorless solution was stirred vigorously for 5 min, before concentrating in vacuo. The residue was purified by column chromatography (EtOAc/Et_3N 8:1) to afford the title compound as a colorless oil (10.70 g, 81%). R_f=0.35 (visualized by ninhydrin spray reagent giving a pink stain). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (t, 2H, J=5.3 Hz), 2.77 (t, 2H, J=5.3 Hz), 1.32 (br s, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.5, 44.6, 26.1 (3C), 18.5, −5.2 (2C). HRMS (APPI): *m/z* calcd for $C_8H_{22}NOSi$ (MH^+) 176.1465, found 176.1463.

4.3.13. 3-Bromo-N-(2-(tert-butyldimethylsilyloxy)ethyl)-aniline (Table 1, entry 7)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and 2-(*tert*-butyldimethylsilyloxy)ethylamine (351 mg, 2 mmol), general procedure A (8 h) afforded the title compound as a colorless oil (388 mg, 58%). R_f=0.27 (heptane/(*i*-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, 1H, *J*=8.0, 8.0 Hz), 6.81 (ddd, 1H, *J*=7.9, 1.8, 0.7 Hz), 6.76 (dd, 1H, *J*=2.1, 2.0 Hz), 6.53 (ddd, 1H, *J*=8.1, 2.2, 0.6 Hz), 4.11 (br s, 1H), 3.80 (t, 2H, *J*=5.4 Hz), 3.18 (td, 2H, *J*=5.4, 5.4 Hz), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 130.6, 123.4, 120.4, 115.8, 112.1, 61.6, 45.9, 26.0 (3C), 18.5, −5.2 (2C). HRMS (ESI): *m/z* calcd for $C_{14}H_{25}BrNOSi$ (MH^+) 330.0883, found 330.0889.

4.3.14. 1-(3-Bromophenyl)pyrrolidine (Table 1, entry 8)

Starting from 1,3-dibromobenzene (472 mg, 2.0 mmol) and pyrrolidine (171 mg, 2.4 mmol, 1.2 equiv), general procedure A (4.5 h) afforded the title compound as a colorless oil (353 mg, 78%). R_f=0.47 (heptane/(*i*-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[30]

4.3.15. 1-(3-Bromo-2-methylphenyl)pyrrolidine (Table 1, entry 8)

Starting from 2,6-dibromotoluene (**2**) (5.00 g, 20 mmol) and pyrrolidine (1.42 g, 20 mmol), general procedure A (2.5 h) afforded the title compound as a colorless oil (3.01 g, 68%). R_f=0.72 (heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, 1H, *J*=7.8 Hz), 6.94 (t, 1H, *J*=8.0 Hz), 6.88 (d, 1H, *J*=8.0 Hz), 3.13−3.07 (m, 4H), 2.37 (s, 3H), 1.96−1.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 129.7, 127.1, 127.0, 125.2, 115.6, 51.6 (2C), 24.9 (2C), 20.2. Anal. Calcd for $C_{11}H_{14}BrN$: C, 55.02; H, 5.88; N, 5.83. Found: C, 55.26; H, 5.87; N, 5.72.

4.3.16. 3-Bromo-N-iso-propylaniline (Table 1, entry 9)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and isopropylamine (118 mg, 2 mmol), general procedure A (4 h) afforded the title compound as a slightly tan oil (288 mg, 67%). R_f=0.44 (heptane/EtOAc 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, 1H, *J*=8.0, 8.0 Hz), 6.76 (ddd, 1H, *J*=7.8, 1.8, 0.9 Hz), 6.70 (dd, 1H, *J*=2.1, 2.0 Hz), 6.47 (ddd, 1H, *J*=8.2, 2.3, 0.8 Hz), 3.58 (septet, 1H, *J*=6.3 Hz), 3.30 (very br s, 1H), 1.20 (d, 6H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 130.6, 123.4, 119.6, 115.6, 112.0, 44.2, 22.9 (2C). HRMS (ESI): *m/z* calcd for $C_9H_{13}BrN$ (MH^+) 214.0226, found 214.0225.

4.3.17. 3-Bromo-N-tert-butylaniline (Table 1, entry 9)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and *tert*-butylamine (146 mg, 2 mmol), general procedure A (23 h) afforded the title compound as a pale yellow oil (231 mg, 51%). R_f=0.21 (heptane/(*i*-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (dd, 1H, *J*=8.0, 8.0 Hz), 6.86 (dd, 1H, *J*=2.1, 2.0 Hz), 6.82 (ddd, 1H, *J*=7.9, 1.8, 0.8 Hz), 6.61 (ddd, 1H, *J*=8.2, 2.3, 0.8 Hz), 3.58 (br s, 1H), 1.34 (s, 9H); ^{1}H NMR in agreement with previously reported[31] data run at lower spectrometer frequency; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 130.3, 123.0, 120.6, 119.1, 115.1, 51.6, 30.0 (3C). HRMS (ESI): *m/z* calcd for $C_{10}H_{15}BrN$ (MH^+) 228.0382, found 228.0381.

4.3.18. N-Allyl-3-bromoaniline (Table 1, entry 9)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and allylamine (114 mg, 2 mmol), general procedure A (5 h) afforded the title compound as a slightly tan oil (209 mg, 49%). R_f=0.26 (heptane/(*i*-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, 1H, *J*=8.0, 8.0 Hz), 6.81 (ddd, 1H, *J*=7.8, 1.8, 0.8 Hz), 6.74 (dd, 1H, *J*=2.1, 2.1 Hz), 6.51 (ddd, 1H, *J*=8.2, 2.3, 0.8 Hz), 5.91 (ddt, 1H, *J*=17.2, 10.3, 5.3 Hz), 5.27 (ddt, 1H, *J*=17.2, 3.2, 1.7 Hz), 5.18 (ddt, 1H, *J*=10.3, 3.0, 1.5 Hz), 3.87 (br s, 1H), 3.74 (ddd, 2H, *J*=5.3, 1.6, 1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 134.8, 130.6, 123.4, 120.3, 116.7, 115.6, 111.8, 46.4. HRMS (ESI): *m/z* calcd for $C_9H_{11}BrN$ (MH^+) 212.0069, found 212.0070.

4.3.19. N-(3-Bromophenyl)-2,6-di-iso-propylaniline (Table 1, entry 10)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and 2,6-di-*iso*-propylaniline (355 mg, 2 mmol), general procedure A (5 h) afforded the title compound as a colorless oil (570 mg, 86%). R_f=0.39 (heptane/(*i*-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, 1H, *J*=8.1, 7.2 Hz), 7.22 (d, 2H, *J*=7.9 Hz), 6.97 (t, 1H, *J*=8.0 Hz), 6.81 (ddd, 1H, *J*=7.9, 1.8, 0.9 Hz), 6.63 (br s, 1H), 6.37 (d, 1H, *J*=7.8 Hz), 5.15 (br s, 1H), 3.15 (septet, 2H, *J*=6.9 Hz), 1.14 (d, 12H, *J*=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 147.7 (2C), 134.3, 130.7, 127.8, 124.2 (2C), 123.4, 120.7, 115.8, 111.6, 28.4 (2C), 24.0 (4C). HRMS (ESI): *m/z* calcd for $C_{18}H_{23}BrN$ (MH^+) 332.1008, found 332.1000.

4.3.20. 3-Bromo-N,N-di-n-propylaniline (Table 1, entry 11)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and dipropylamine (202 mg, 2 mmol), general procedure A (20 h) afforded the title compound as a pale yellow oil (261 mg, 51%). R_f=0.68 (heptane/EtOAc 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dd, 1H, *J*=8.3, 7.9 Hz), 6.75−6.69 (m, 2H), 6.53 (ddd, 1H, *J*=8.3, 2.5, 0.5 Hz), 3.20 (t, 4H, *J*=7.7 Hz), 1.59 (tq, 4H, *J*=7.7, 7.4 Hz), 0.92 (t, 6H, *J*=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 130.5, 123.7, 118.0, 114.4, 110.4, 52.9 (2C), 20.4 (2C), 11.5 (2C). HRMS (ESI): *m/z* calcd for $C_{12}H_{19}BrN$ (MH^+) 256.0695, found 256.0697.

4.3.21. 1-(3-Bromo-2-methylphenyl)piperidine (Table 1, entry 12)

Starting from 2,6-dibromotoluene (**2**) (5.00 g, 20 mmol) and piperidine (1.70 g, 20 mmol), general procedure A (3.5 h) afforded the title compound as a colorless oil (4.26 g, 84%). R_f=0.52 (heptane/EtOAc 50:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, 1H, *J*=7.8, 1.1 Hz), 6.99 (t, 1H, *J*=7.9 Hz), 6.94 (dd, 1H, *J*=7.9, 1.0 Hz), 2.80 (br s, 4H), 2.37 (s, 3H), 1.71 (pentet, 4H, *J*=5.5 Hz), 1.57 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 133.0, 127.3, 126.9, 126.5, 118.2, 53.8 (2C), 26.6 (2C), 24.4, 18.4. Anal. Calcd for $C_{12}H_{16}BrN$: C, 56.71; H, 6.35; N, 5.51. Found: C, 56.57; H, 6.23; N, 5.47.

4.3.22. tert-Butyl 4-(3-bromo-2-methylphenyl)piperazine-1-carboxylate (Table 1, entry 13)

Starting from 2,6-di-bromotoluene (**2**) (7.50 g, 30 mmol) and *tert*-butyl piperazine-1-carboxylate (5.59 g, 30 mmol), general procedure A (3 h) afforded the title compound as an oil, solidifying on standing to afford a yellow solid (8.69 g, 82%). R_f=0.40 (heptane/EtOAc 6:1). An analytically pure sample was obtained by recrystallization as a colorless transparent powder, mp 71.5–72.2 °C (heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, 1H, J=8.0, 0.6 Hz), 7.02 (t, 1H, J=8.0 Hz), 6.94 (d, 1H, J=8.0 Hz), 3.57 (br s, 4H), 2.82 (br s, 4H), 2.39 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 153.0, 133.1, 127.9, 127.5, 126.7, 118.4, 80.0, 52.2 (2C), 44.7 (br s, 2C, rotamer), 28.6 (3C), 18.4. Anal. Calcd for $C_{16}H_{23}BrN_2O_2$: C, 54.09; H, 6.53; N, 7.89. Found: C, 54.35; H, 6.54; N, 7.82.

4.3.23. 4-(3-Bromo-2-methylphenyl)thiomorpholine (Table 1, entry 13)

Starting from 2,6-dibromotoluene (**2**) (5.00 g, 20 mmol) and thiomorpholine (2.07 g, 20 mmol), general procedure A (16 h) afforded the title compound as an oil, solidifying on standing to afford a white solid (4.50 g, 83%). R_f=0.23 (heptane). An analytically pure sample was obtained by recrystallization as a bright-white powder, mp 54.0–54.6 °C (heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, 1H, J=7.9, 1.1 Hz), 7.02 (t, 1H, J=7.9 Hz), 6.96 (dd, 1H, J=8.0, 1.1 Hz), 3.18–3.06 (m, 4H), 2.80 (br s, 4H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 133.4, 127.9, 127.5, 126.5, 119.2, 54.8 (2C), 28.5 (2C), 18.3. Anal. Calcd for $C_{11}H_{14}BrNS$: C, 48.54; H, 5.18; N, 5.15; S, 11.78. Found: C, 48.69; H, 5.23; N, 5.16; S, 11.56.

4.3.24. cis-4-(3-Bromo-2-methylphenyl)-2,6-dimethylmorpholine (Table 1, entry 14)

Starting from 2,6-dibromotoluene (**2**) (5.00 g, 20 mmol) and *cis*-2,6-dimethylmorpholine (2.31 g, 20 mmol), general procedure A (5 h) afforded the title compound as a faintly yellow oil (4.30 g, 76%). R_f=0.23 (heptane/EtOAc 25:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, 1H, J=7.9 Hz), 7.02 (t, 1H, J=8.0 Hz), 6.95 (d, 1H, J=8.0 Hz), 3.89–3.81 (m, 2H), 2.89 (d, 2H, J=11.1 Hz), 2.42 (dd, 2H, J=11.5, 10.3 Hz), 2.38 (s, 3H), 1.21 (d, 6H, J=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 133.0, 127.7, 127.5, 126.7, 118.3, 72.2 (2C), 58.3 (2C), 19.1 (2C), 18.4. Anal. Calcd for $C_{13}H_{18}BrNO$: C, 54.94; H, 6.38; N, 4.93. Found: C, 55.01; H, 6.18; N, 5.05.

4.3.25. 3-Bromo-N-cyclo-hexyl-N-methylaniline (Table 1, entry 15)

Starting from 1,3-dibromobenzene (472 mg, 2 mmol) and *N*-methylcyclohexylamine (226 mg, 2 mmol), general procedure A (20 h) afforded the title compound as a pale yellow oil (204 mg, 38%). R_f=0.87 (toluene). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (dd, 1H, J=8.4, 7.9 Hz), 6.85 (dd, 1H, J=2.3, 2.1 Hz), 6.77 (ddd, 1H, J=7.8, 1.8, 0.8 Hz), 6.66 (dd, 1H, J=8.4, 2.3 Hz), 3.51 (tt, 1H, J=11.4, 3.5 Hz), 2.75 (s, 3H), 1.89–1.80 (m, 2H), 1.79–1.72 (m, 2H), 1.72–1.65 (m, 1H), 1.50–1.30 (m, 4H), 1.19–1.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 130.4, 123.6, 118.8, 115.6, 111.5, 58.1, 31.2, 30.2 (2C), 26.2 (2C), 26.0. HRMS (ESI): *m/z* calcd for $C_{13}H_{19}BrN$ (MH^+) 268.0695, found 268.0697.

4.3.26. 4-Bromo-N-cyclo-hexylaniline (Table 1, entry 16)

Starting from 1,4-dibromobenzene (472 mg, 2 mmol) and cyclohexylamine (198 mg, 2 mmol), general procedure A (3 h) afforded the title compound as a pale yellow solid (437 mg, 86%). R_f=0.28 (heptane/(i-Pr)$_2$O 40:3). An analytically pure sample was obtained by recrystallization as a white powder, mp 57.9–59.3 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, 2H, J=8.9 Hz), 6.45 (d, 2H, J=8.9 Hz), 3.56 (br s, 1H), 3.19 (tt, 1H, J=10.2, 3.8 Hz), 2.09–1.96 (m, 2H), 1.81–1.70 (m, 2H), 1.69–1.58 (m, 1H), 1.42–1.29 (m, 2H), 1.28–1.05 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 132.0 (2C), 114.8 (2C), 108.3, 51.9, 33.4 (2C), 26.0, 25.1 (2C). Anal. Calcd for $C_{12}H_{16}BrN$: C, 56.71; H, 6.35; N, 5.51. Found: C, 56.62; H, 6.38; N, 5.39.

4.3.27. N-Benzyl-4-bromoaniline (Table 1, entry 17)

Starting from 1,4-dibromobenzene (472 mg, 2 mmol) and benzylamine (214 mg, 2 mmol), general procedure A (4 h) afforded the title compound as a colorless oil (374 mg, 71%). R_f=0.23 (heptane/(i-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[32]

4.3.28. N-(4-Bromophenyl)-4-methoxy-2-methylaniline (Table 1, entry 18)

Starting from 1,4-dibromobenzene (472 mg, 2 mmol) and 4-methoxy-2-methylaniline (274 mg, 2 mmol), general procedure A (14 h) afforded the title compound as a yellow-orange, viscous oil (443 mg, 76%). R_f=0.22 (heptane/TBME 10:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.48 (br s, 1H), 7.22 (d, 2H, J=8.9 Hz), 7.05 (d, 1H, J=8.6 Hz), 6.85 (d, 1H, J=3.0 Hz), 6.75 (dd, 1H, J=8.6, 3.0 Hz), 6.55 (d, 2H, J=8.9 Hz), 3.73 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.1, 146.6, 134.5, 132.9, 131.5 (2C), 125.8, 116.1, 115.4 (2C), 111.9, 107.6, 55.1, 18.0. HRMS (ESI): *m/z* calcd for $C_{14}H_{15}BrNO$ (MH^+) 292.0332, found 292.0328.

4.3.29. N-(4-Bromophenyl)-N-ethylbenzo[d][1,3]dioxol-5-amine (Table 1, entry 19)

Starting from 1,4-dibromobenzene (472 mg, 2 mmol) and *N*-ethyl-3,4-methylenedioxyaniline (330 mg, 2 mmol), general procedure A (16 h) afforded the title compound as a colorless oil (456 mg, 71%). R_f=0.38 (heptane/(i-Pr)$_2$O 40:3). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26–7.19 (m, 2H), 6.78 (dd, 1H, J=8.2, 1.3 Hz), 6.65–6.54 (m, 4H), 5.96 (s, 2H), 3.62 (q, 2H, J=7.1 Hz), 1.17 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.6, 147.8, 145.0, 141.2, 131.8 (2C), 119.7, 117.1 (2C), 109.9, 108.9, 108.0, 101.5, 46.8, 12.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{15}BrNO_2$ (MH^+) 320.0281, found 320.0277.

4.3.30. *tert*-Butyl 4-(2-methyl-3-morpholinophenyl)piperazine-1-carboxylate (**6**)

4-(3-Bromo-2-methylphenyl)morpholine (**1**) (9.77 g, 38 mmol) and *tert*-butyl piperazine-1-carboxylate (8.53 g, 46 mmol) were added to a flask containing Pd_2dba_3 (2.5%), P(*t*-Bu)$_3\cdot HBF_4$ (5%), and NaO(*t*-Bu) (1.4 equiv). Toluene (100 mL) and a stir bar were added. The head space was purged with N_2 and a positive pressure of N_2 applied throughout the reaction, but the solvent was not degassed. The mixture was stirred at 80 °C for 2 h. After cooling to rt, Et_2O was added (100 mL) before filtering through a pad of Celite. The filtrate was concentrated in vacuo onto silica and purified by chromatography to afford the title compound as a pale yellow solid (12.83 g, 93%). R_f=0.23 (heptane/EtOAc 6:1). An analytically pure sample was obtained by recrystallization from pentane as fine bright-white needles, mp 109.4–110.3 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, 1H, J=8.0 Hz), 6.79 (d, 1H, J=8.0 Hz), 6.76 (d, 1H, J=8.0 Hz), 3.87–3.82 (m, 4H), 3.56 (br s, 4H), 2.94–2.89 (m, 4H), 2.89–2.81 (m, 4H), 2.30 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 152.8, 152.8, 127.2, 126.8, 114.3, 114.2, 79.8, 67.6 (2C), 52.4 (2C), 52.0 (2C), 44.7/43.9 (2C, rotamer), 28.6 (3C), 13.3. Anal. Calcd for $C_{20}H_{31}N_3O_3$: C, 66.45; H, 8.64; N, 11.62. Found: C, 66.57; H, 8.56; N, 11.60.

4.3.31. 3-(3-Bromopropyl)-5-fluoro-1H-indole (**7**)

Adopting Campos et al.'s procedure,[33] 4-fluorophenylhydrazine hydrochloride (15.0 g, 92 mmol) was added to a three-necked reaction flask equipped with stir bar, condenser, and septa, and a positive pressure of N_2 was applied. DMA (150 mL) was added while stirring. Next, 4% aq H_2SO_4 (150 mL) was added, and the reaction mixture was heated to 100 °C. 3,4-Dihydro-2*H*-pyran (8.4 mL, 92 mmol) was added drop-wise using a syringe. After full conversion of the starting materials (as judged by TLC, ~4 h), the reaction mixture was cooled to rt and extracted with EtOAc (3×300 mL). The combined organic extracts were washed with H_2O (3×300 mL). The organic layer was concentrated in vacuo, and the residue was purified by chromatography to afford 3-(5-fluoro-1*H*-indol-3-yl)propan-1-ol as an orange, highly viscous oil (14.72 g, 83%). R_f=0.25 (heptane/EtOAc 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[33] Under a positive pressure of N_2, 3-(5-fluoro-1*H*-indol-3-yl)propan-1-ol (14.45 g, 75 mmol) was dissolved in acetonitrile (150 mL), and PPh_3 (29.5 g, 112.5 mmol) was added to form a suspension. After cooling to 0 °C, CBr_4 (37.3 g, 112.5 mmol) was added portion-wise over a 10-min period. After full conversion (~3 h), the reaction mixture was adsorbed on silica. Chromatography afforded the title compound as a yellow oil (11.50 g, 60%). The compound solidified upon storage at −20 °C as a brown solid, mp below rt. R_f=0.21 (heptane/EtOAc 6:1). ^{1}H NMR (500 MHz, DMSO-d_6) in agreement with the literature.[34] ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.7 (d, J=231.1 Hz), 133.0, 127.3 (d, J=9.6 Hz), 124.7, 113.1 (d, J=4.6 Hz), 112.3 (d, J=9.7 Hz), 109.0 (d, J=26.0 Hz), 102.9 (d, J=22.8 Hz), 34.9, 33.0, 23.0.

4.3.32. 4-(3-(4-(3-(5-Fluoro-1H-indol-3-yl)propyl)piperazin-1-yl)-2-methylphenyl)morpholine (***Lu 37-211***)

tert-Butyl 4-(2-methyl-3-morpholinophenyl)piperazine-1-carboxylate (**6**) (1.084 g, 3 mmol) was dissolved in a minimum volume of MeOH/Et_2O and stirred at rt. In the meanwhile, MeOH (30 mL) was rapidly stirred at 0 °C, and AcCl (10–15 equiv) was *cautiously* added drop-wise. The methanolic HCl was added to the solution of **6**, stirring until full conversion according to TLC. After full conversion of the starting material, the reaction mixture was concentrated in vacuo. The crude hydrochloride salt was resuspended in 2–3 mL of saturated brine, and the mixture was made alkaline (pH ~12) with 24% aq NH_3. The resulting mixture was exhaustively extracted with THF. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The free base was used directly in the next step. The free base was reacted with **7** (768 mg, 3 mmol) in the presence of DIPEA (1.5 equiv) in acetonitrile (40 mL) under N_2 and heated (70–80 °C) with stirring until full conversion of starting materials (24 h) as determined by TLC. After concentration in vacuo on silica, chromatography afforded **Lu 37-211** as a colorless, solid foam (1.22 g, 93%). R_f=0.25 (heptane/EtOAc/Et_3N 49:49:2). An analytically pure sample was obtained by crystallization as a white powder, mp 126.0–126.6 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.28–7.22 (m, 2H), 7.15 (t, 1H, J=8.0 Hz), 7.03 (d, 1H, J=2.1 Hz), 6.93 (td, 1H, J=9.0, 2.5 Hz), 6.80 (d, 1H, J=8.0 Hz), 6.76 (d, 1H, J=7.0 Hz), 3.87–3.82 (m, 4H), 3.00–2.93 (m, 4H), 2.93–2.88 (m, 4H), 2.76 (t, 2H, J=7.6 Hz), 2.62 (br s, 4H), 2.50 (t, 2H, J=7.6 Hz), 2.38 (s, 3H), 1.94 (pentet, 2H, J=7.6 Hz); ^{13}C (125 MHz, $CDCl_3$) δ 157.8 (d, J=234.2 Hz), 153.0, 152.6, 133.0, 128.1, 127.0, 126.7, 123.1, 116.9, 114.2, 113.7, 111.7 (d, J=9.6 Hz), 110.4 (d, J=26.4 Hz), 104.0 (d, J=23.2 Hz), 67.6 (2C), 58.6, 54.0 (2C), 52.4 (2C), 51.9 (2C), 27.5, 23.1, 13.4. Anal. Calcd for $C_{26}H_{33}FN_4O$: C, 71.53; H, 7.62; N, 12.83. Found: C, 71.73; H, 7.55; N, 12.80.

4.4. General procedure B

Equivalent to general procedure A with the following modifications: Xantphos (116 mg, 10 mol %) as ligand; amine or imine (2.0–2.4 mmol, 1.0–1.2 equiv).

4.4.1. 1-(4-Bromo-2-methylphenyl)piperidine (Table 2, entry 1)

Starting from 4-bromo-1-iodo-2-methylbenzene (594 mg, 2 mmol) and piperidine (170 mg, 2 mmol), general procedure B (2.5 h) afforded the title compound as a colorless oil (365 mg, 72%). R_f=0.48 (heptane/(*i*-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 (d, 1H, J=2.5 Hz), 7.27 (dd, 1H, J=8.5, 2.4 Hz), 6.91 (d, 1H, J=8.5 Hz), 2.73 (dd, 4H, J=5.2, 5.0 Hz), 2.21 (s, 3H), 1.69–1.57 (m, 4H), 1.56–1.44 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.1, 135.2, 133.6, 129.3, 120.8, 115.5, 53.4 (2C), 26.6 (2C), 24.4, 17.8. HRMS (ESI): *m/z* calcd for $C_{12}H_{17}BrN$ (MH^+) 254.0539, found 254.0538.

4.4.2. 4-(4-Bromo-2-fluorophenyl)morpholine (Table 2, entry 2)

Starting from 4-bromo-2-fluoro-1-iodobenzene (602 mg, 2 mmol) and morpholine (174 mg, 2 mmol), general procedure B (1 h) afforded the title compound as a colorless oil (459 mg, 88%). R_f=0.33 (heptane/(i-Pr)$_2$O 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2H), 6.80 (dd, 1H, J=8.8, 8.6 Hz), 3.88–3.84 (m, 4H), 3.07–3.03 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (d, J=250.9 Hz), 139.4 (d, J=8.3 Hz), 127.7 (d, J=3.3 Hz), 119.9, 119.8 (d, J=19.4 Hz), 114.0 (d, J=9.5 Hz), 67.0 (2C), 50.9 (2C). HRMS (ESI): m/z calcd for $C_{10}H_{12}BrFNO$ (MH^+) 260.0081, found 260.0079.

4.4.3. N-Allyl-4-bromo-2-chloroaniline (Table 2, entry 3)

Starting from 4-bromo-2-chloro-1-iodobenzene (635 mg, 2 mmol) and allylamine (137 mg, 2 mmol), general procedure B (0.5 h) afforded the title compound as a colorless oil (444 mg, 90%). R_f=0.46 (heptane/(i-Pr)$_2$O 40:3). ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) in agreement with the literature.[35]

4.4.4. 4-Bromo-N-(4-bromophenyl)-2-chloroaniline (Table 2, entry 4)

Starting from 4-bromo-2-chloro-1-iodobenzene (635 mg, 2 mmol) and 4-bromoaniline (413 mg, 2.4 mmol), general procedure B (0.5 h) afforded the title compound as an off-white solid (697 mg, 96%). R_f=0.48 (heptane/(i-Pr)$_2$O 40:3). An analytically pure sample was obtained by recrystallization as a bright-white powder, mp 84.8–85.8 °C (MeOH). ^{1}H NMR (500 MHz, CD_3CN) and ^{13}C NMR (125 MHz, CD_3CN) in agreement with the literature.[36] Anal. Calcd for $C_{12}H_8Br_2ClN$: C, 39.87; H, 2.23; N, 3.88. Found: C, 39.80; H, 2.15; N, 3.83.

4.4.5. N′-(2-Bromo-5-fluoro-phenyl)-N,N-dimethyl-ethane-1,2-diamine (Table 2, entry 5)

Starting from 1-bromo-4-fluoro-2-iodobenzene (11.9 g, 39.5 mmol) and *N*,*N*-dimethyl-ethylenediamine (3.66 g, 41.5 mmol), general procedure B (40 h; 0.5% Pd_2dba_3, 2.0% Xantphos, 100 mL toluene). The crude mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The organic layer was extracted with 10% HCl (200 mL). The aqueous layer was basified with NaOH and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound as a pale brown oil (8.52 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, 1H, J=6.05, 8.70 Hz), 6.33–6.24 (m, 2H), 5.04 (br s, 1H), 3.31 (app. q, 2H, J=10.9 Hz), 2.59 (t, 2H, J=6.15 Hz), 2.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (d, J=243.1 Hz), 147.0 (d, J=11.2 Hz), 133.2 (d, J=10.4 Hz), 104.2 (d, J=23.4 Hz), 104.1 (d, J=2.6 Hz), 99.0 (d, J=26.7 Hz), 57.9, 45.6 (2C), 41.5. HRMS (ESI): m/z calcd for $C_{10}H_{14}BrFN_2$ (MH^+) 261.0397, found 261.0395.

Acknowledgements

We thank Dr. Henrik Pedersen and Dr. Jens Christian Madsen (Medicinal Chemistry Research, H. Lundbeck A/S) for performing high-resolution MS and for assisting with NMR spectroscopy.

References and notes

1. For a general discussion, see: *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
2. (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612; (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350; For reviews, see: (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626; (d) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23–39; (e) Hartwig, J. F. *Palladium-Catalyzed Amination of Aryl Halides and Related Reactions*; Negishi, E., Ed.; Handbook of Organopalladium Chemistry for Organic Synthesis; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, pp 1051–1096.
3. Kondratenko, N. V.; Kolomeitsev, A. A.; Mogilevskaya, V. O.; Varlamova, N. M.; Yagupol'skii, L. M. *Zh. Org. Khim.* **1986**, *22*, 1721–1729; *J. Org. Chem., USSR (Engl. Transl.)* **1986**, *22*, 1547–1554.
4. Selective monoamination of dihalogenated benzenes has mostly been limited to couplings of aryl iodides or nonaflates in preference to bromides. See for example: (a) Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563–9573; (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066–6068; For studies of the reaction involving mainly acyclic polyamines, see: (c) Beleskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Synlett* **1999**, 1459–1462; (d) Beleskaya, I. P.; Bessmertnykh, A. G.; Averin, A. D.; Denat, F.; Guilard, R. *Eur. J. Org. Chem.* **2005**, 261–280.
5. This notion has been nicely described by Crabtree: 'Homogeneous catalyst discovery owes at least as much to emperical testing as to mechanistic understanding, because structure/function relationships are either obscure or not readily predictable for most catalysts'; Crabtree, R. H. *Chem. Commun.* **1999**, 1611–1616.
6. All experiments were performed without drybox or Schlenk techniques. Chemicals were weighed out in air, and no precautions were undertaken to exclude air from the reaction mixture. Toluene was stored over 4 Å molecular sieves and used without further purification or degassing.
7. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.
8. (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216; (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
9. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327–5330.
10. For an overview of the Buchwald ligands, see: Jiang, L.; Buchwald, S. L. Palladium-Catalyzed Aromatic Carbon–Nitrogen Bond Formation. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 699–760.
11. Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569.
12. (a) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729–7737; (b) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307–1309.
13. Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423–1426.
14. (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617–620; (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580; (c) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.
15. Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789–3790.
16. Jamie-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313–1316.

17. (a) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367–6370; (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
18. Ruhland, T.; Bang, K. S.; Andersen, K. *J. Org. Chem.* **2002**, *67*, 5257–5268.
19. Xantphos has been applied previously in the amination of aryl iodides. See for example: Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565.
20. (a) Mellesham, B.; Rajesh, B. M.; Rajamohan Reddy, P.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963–965; (b) Einsidel, J.; Schoerner, C.; Gmeiner, P. *Tetrahedron* **2003**, *59*, 3404–3408.
21. Katsifis, A. G.; McPhee, M. E.; Mattner, F.; Ridley, D. D. *Aust. J. Chem.* **1999**, *52*, 1061–1070.
22. Hartwell, J. L. *Org. Synth., Coll. Vol. III* **1955**, 185–189.
23. Iwasaki, T.; Kohinata, Y.; Nishide, H. *Org. Lett.* **2005**, *7*, 755–758.
24. Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269–276.
25. Johansson, G.; Sundquist, S.; Nordvall, G.; Nilsson, B. M.; Brisander, M.; Nilvebrant, L.; Hacksell, U. *J. Med. Chem.* **1997**, *40*, 3804–3819.
26. Jones, D. H. *J. Chem. Soc. C* **1971**, 132–137.
27. Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985–987.
28. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
29. Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 4960–4976.
30. Verardo, G.; Dolce, A.; Toniutti, N. *Synthesis* **1999**, 74–79.
31. Calder, A.; Forrester, A. R.; Hepburn, S. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 456–465.
32. (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5177; (b) Carboni, B.; Vaultier, M.; Courgeon, T.; Carrié, R. *Bull. Soc. Chim. Fr.* **1989**, *6*, 844–849.
33. Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79–82.
34. Mewshaw, R. E.; Zhou, D.; Zhou, P.; Shi, X.; Hornby, G.; Spangler, T.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *J. Med. Chem.* **2004**, *47*, 3823–3842.
35. Yang, S.-C.; Hung, C.-W. *Synthesis* **1999**, 1747–1752.
36. Winter, A. H.; Thomas, S. I.; Kung, A. C.; Falvey, D. E. *Org. Lett.* **2004**, *6*, 4671–4674.