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Mild conditions for Pd-catalyzed conversion of aryl bromides to primary anilines using benzophenone imine

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ABSTRACT

Mild (30 °C) and efficient (53–91%) conversion of aryl bromides to primary anilines using a Pd-catalyzed amination strategy is described. A detailed account of the ligand optimization, base and solvent selection, and general substrate scope of this methodology is described herein.

The area of palladium-catalyzed C_{aryl}–N bond formation has received increased attention in the last decade,[1] particularly in medicinal chemistry applications.[2] The conversion of aryl halides and their equivalents to primary aniline derivatives is a useful subset of Pd-catalyzed amination reactions. There have been several reports that utilize benzophenone imine,[3] *tert*-butyl carbamate,[4] lithium bis(trimethylsilyl)amide[5], and lithium amide[6] as ammonia equivalents. In the last two years, Hartwig[6] and Buchwald[7] have demonstrated the use of ammonia itself in the amination of aryl halides. In 2005, Hartwig reported room-temperature aminations of *activated* aryl bromides in the presence of in situ generated zinc bis(hexamethyldisilylamide).[8] While steady progress has been made in the field, particularly in the area of atom economy, reaction conditions remain relatively harsh, requiring strong bases and/or elevated temperatures. Furthermore, despite the subsequent popularity of benzophenone imine as an ammonia equivalent, to our knowledge, no systematic optimization of this reaction has been reported since the initial disclosure. We set out to explore the potential of this conversion to be conducted under mild conditions, closer to room temperature, and in the presence of a weak inorganic base.

Our first objective was to determine an efficacious combination of ligand and Pd pre-catalyst. In addition to standard ligands such as tri-*tert*-butylphosphine (Fig. 1, **19**) and Xantphos (Fig. 1, **11**), we were interested in pursuing the use of monodentate biaryl ligands reported by Buchwald[9] and Beller[10] for aminations and other mild cross-coupling reactions. These bulky monophosphinobiaryl ligands form active and effective catalyst systems with different Pd sources.[11,12] Therefore, ligand selection (Fig. 1) for our screening was based on commercial availability and literature precedent for promoting amination of aryl halides in the presence of weak bases or at lower temperatures.

Table 1 summarizes the ligand screen using standard literature conditions[3a] (substrate **1**, benzophenone imine **2**, $Pd_2dba_3{\cdot}CHCl_3$ as the pre-catalyst, sodium *tert*-butoxide as the base, toluene as solvent). We set the initial temperature at 65 °C, with the intention of repeating successful reactions at a lower temperature. Conversion to product **3** was monitored by GC/MS. From this screening, ligands **8**, **10–12**, and **18** (entries 5, 7–9, and 15) showed the highest GC conversions in the shortest times. In the case of ligand **12** (entry 9), the reaction was complete as determined by GC/MS in <1 h. We then focused our screening on ligands **8**, **10–12**, and **18,** and lowered the temperature to room temperature. Ligand **12** (entry 20) gave complete GC conversion to product in just over 4 h. Ligand **18**, which has recently shown to be outstanding in its C_{aryl}-N and C_{aryl}–O-bond formation capability,[13,14] gave no product at room temperature (Table 1, entry 21).

Base optimization in the presence of ligand **12** at different temperatures is shown in Table 2. Complete conversion was observed with NaO*t*Bu at 65 °C, 45 °C, and room temperature (Table 2, entries 1–3). In the presence of weak, inorganic bases such as Cs_2CO_3, KOAc, CsF, and K_3PO_4 (entries 4, 6–8), however, the reaction gave poor conversions. K_2CO_3 (entry 5) was an exception, which

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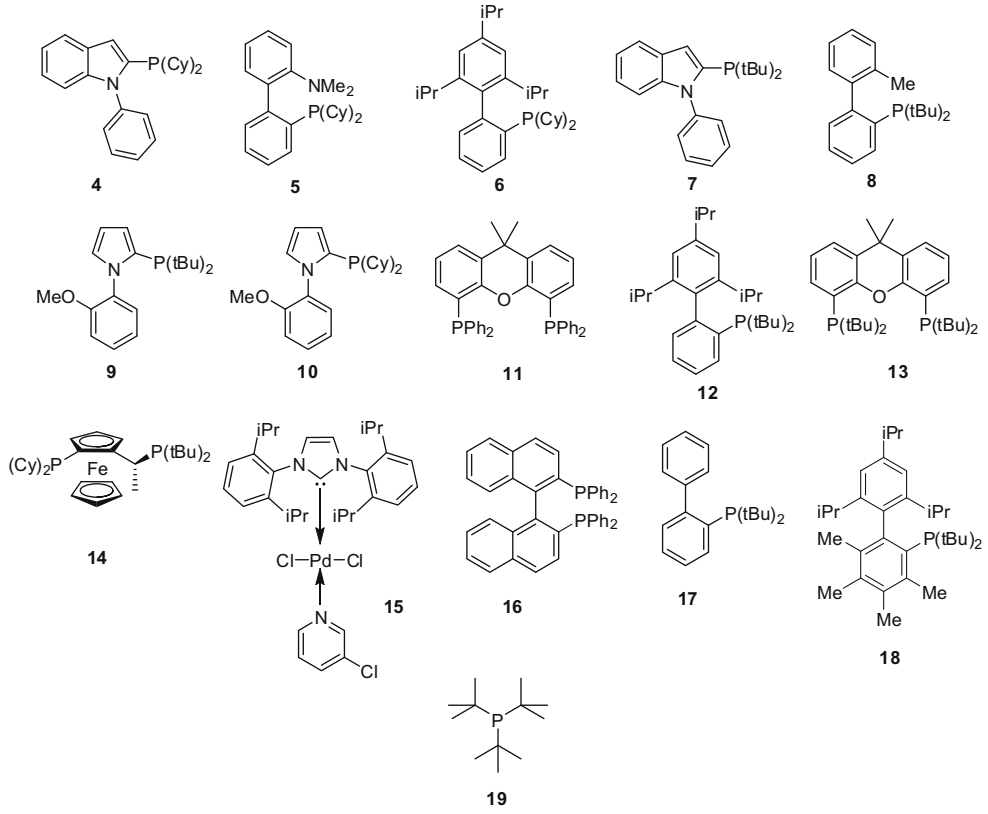
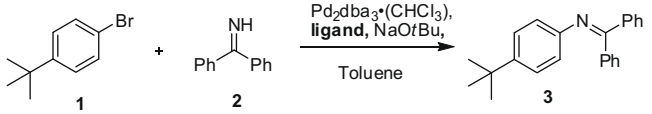


Figure 1. Ligands surveyed.

Table 1
Ligand optimization with benzophenone imine as ammonia equivalent[a]

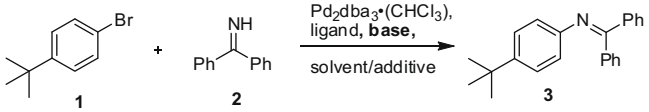


1 2 3

Entry	Ligand	Temp (°C)	Time (h)	GC conversion (%)
1	**4**	65	18	0
2	**5**	65	22	<5
3	**6**	65	6.5	50
4	**7**	65	6	100
5	**8**	65	4.5	100
6	**9**	65	3	95:5[b]
7	**10**	65	2	100
8	**11**	70	2	100
9	**12**	65	0.5	100
10	**13**	65	2	0
11	**14**	65	2	<5
12[c]	**15**	65	72	0
13	**17**	65	4.5	67
14[d]	**16**	80	16	100
15	**18**	65	5.5	100
16[e]	**19**	65	24	0
17	**8**	rt[f]	16.5	0
18	**10**	rt[f]	16.5	0
19	**11**	rt[f]	16.5	0
20	**12**	**rt[f]**	**4.5**	**100**
21	**18**	rt[f]	48	0

[a] Reaction conditions: 1.3 mmol substrate, 1.2 equiv **2**, 1.4 equiv NaO^{t}Bu, 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 6 mol % ligand, 0.5 M in toluene.
[b] 95:5-desired product: unidentified side product.
[c] 2 mol % **15**, no ligand.
[d] 1 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 3 mol % ligand.
[e] 1:1 Pd:ligand ratio used; 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 4 mol % P(^{t}Bu)$_3$.
[f] rt = 17–22 °C.

Table 2
Optimization of base and solvent[a]



1 2 3

Entry	Base (Additive)[b]	Temp (°C)	Solvent	Time (h)	GC Conversion (%)
1	NaO*t*Bu	65	PhMe	0.5	100
2	NaO*t*Bu	45	PhMe	2.5	100
3	NaO*t*Bu	rt	PhMe	4.5	100
4	Cs_2CO_3	30	PhMe	22	20
5[c]	K_2CO_3	30	PhMe	41	100
6	KOAc	rt to 65	PhMe	22	10
7	CsF	rt to 65	PhMe	22	32
8	K_3PO_4	rt to 65	PhMe	22	40
9[d]	NEt_3	rt to 45	PhMe	22	0
10[d]	DBU	rt to 45	PhMe	22	0
11[d]	DABCO	rt to 45	PhMe	22	0
12[e]	K_3PO_4/ 18-crown-6	65	PhMe	1.5	100
13[c,e]	K_3PO_4/ 18-crown-6	rt to 45	PhMe	24	100
14	K_3PO_4	45	DME	22	100
15[c]	**K_3PO_4**	**30**	**DME**	**28**	**100**
16[c]	K_3PO_4	30	DMF	41	100
17[c]	K_3PO_4	30	1,4-dioxane	41	100
18[c]	K_3PO_4	30	THF	41	100

[a] Reaction conditions: 1.3 mmol substrate, 1.2 equiv **2**, 2.5 equiv base, 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 6 mol % ligand **12**, 0.5 M solvent.
[b] K_2CO_3,Cs_2CO_3, and K_3PO_4 were ground finely using a mortar and pestle before use.
[c] An extra 1 mol % and 3 mol % each of the catalyst and ligand were added after 24 h.
[d] 1.4 equiv organic base.
[e] Recrystallized from hot CH_3CN, 1.0 equiv used with respect to base.

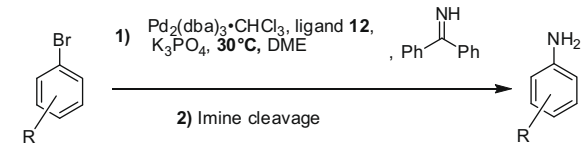
afforded complete conversion after a prolonged reaction time (41 h). For K_3PO_4, when no conversion was observed at room temperature after 6–8 h, the reaction was warmed to 65 °C. However, low conversion was observed even at elevated temperature (entry 8). Hypothesizing that the low solubility of inorganic bases in toluene was responsible for the low conversions, we explored the use of soluble organic bases such as NEt_3, DBU, and DABCO (entries 9–11). In the present case, however, these bases afforded no conversion to product. The use of an additive was explored next. Stoichiometric amounts of the crystalline acetonitrile complex of 18-crown-6[15,16] along with K_3PO_4 gave complete conversion in less than 2 h at 65 °C (Table 2, entry 12). A solvent change from toluene to 1,2-dimethoxyethane (DME) obviated the need for 18-crown-6 and gave high conversions at low temperatures (entries 14–15). Product formation was observed when other polar solvents, such as DMF, 1,4-dioxane, and THF, were used (entries 16–18). Complete conversion, however, took longer in the presence of these solvents (41 h vs 28 h). Reactions were also evaluated in separate cases in the absence of the Pd precatalyst, ligand **12**, and base. No product was detected after 24 h in all three control experiments. Reducing Pd and ligand loading lower than 2 mol % and 6 mol %, respectively, reduced the conversion of the test substrate. The optimal reaction condition is shown in entry 15.

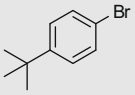
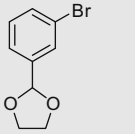
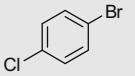
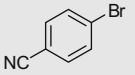
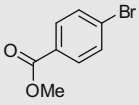
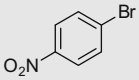
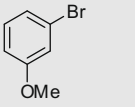
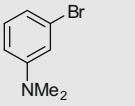
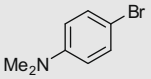
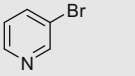
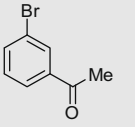
The scope of the optimized conditions with aryl bromide substrates is shown in Table 3.[17,18] The intermediate ketimines were cleaved after minimal work-up (filtration and solvent evaporation) and the reported yields are obtained over two steps. Product yields were lower when the intermediate benzophenone imine was isolated by flash chromatography as compared to cases where the intermediate was not purified. It is hypothesized especially in the case of the electron-poor substrates (e.g., Table 3, entry 6) that the intermediate imine is unstable on silica gel.

In general, 3- and 4-substituted aryl bromides were successfully converted to the corresponding anilines. In particular, the methyl 4-benzoate (entry 5) reacted in 28 h to give an excellent two-step yield of 91%. 4-Nitrobromobenzene (entry 6) and 4-cyanobromobenzene (entry 4) also reacted favorably. An aryl bromide containing enolizable hydrogens (entry 11) was selectively converted to the primary aniline; α-arylation of the ketone was not observed.[5a] The reaction was also selective for the bromide in the presence of a chloride (entry 3). Aryl bromides containing protected aldehydes (entry 2) could also be converted to the primary aniline. Electron-rich substrates (entries 7–9) required longer reaction times for complete conversion and the 4-*N*,*N*-dimethyl substrate required increased catalyst and ligand loading (5 and 15 mol %, respectively). A heteroaromatic bromide (entry 10) was also converted to the primary aniline under these reaction conditions. Particularly for base-sensitive substrates (e.g., entries 5 and 11), this method shows improved substrate scope over the original report.[3a] In the original method, such products were formed under milder conditions (Cs_2CO_3, 65 °C) only by use of more reactive (and more costly) aryl triflate substrates, which further require an additional synthetic step to prepare. The single instance of a base-sensitive aryl bromide coupled with a mild base (Cs_2CO_3) in this Letter required elevated temperature (100 °C).

Ligand **12** is the *tert*-butyl analog of X-Phos (ligand **6**), another commercially available ligand that is considered exceptional in C_{aryl}–N coupling reactions. For cross-coupling reactions in general, studies have demonstrated that increasing ligand bulk leads to more effective reactions, presumably due to an increase in the rate of reductive elimination.[19] Comparing the conversions observed in the present process with the series of ligands **6**, **12**, and **18**, ligand **12** appears to offer the optimal bulk to most efficiently promote both oxidative addition and reductive elimination. This order of activity closely mirrors that observed by Buchwald for the formation of *ortho*-substituted biaryl ethers,[14] and is perhaps a consequence of the substantial steric bulk of benzophenone imine as a nucleophile.

Table 3
Substrate scope of C–N coupling of benzophenone imine using $Pd_2dba_3{\cdot}CHCl_3$ and ligand **12**[a]



Entry	Substrate	Time[b]	Cleavage of imine[c]	Yield[d] (%)
1		24 h	**A**	72
2		42 h	**C**	58
3		28 h	**B**	70
4		44 h	**B**	81
5[e]		28 h	**B**	91
6[e]		24 h	**B**	63
7		48 h	**B**	57
8		52 h	**B**	53
9[f]		7 d	**B**	82
10		28 h	**B**	67
11		42 h	**B**	74

[a] Reaction conditions: 1.3 mmol substrate, 1.2 equiv **2**, 2.5 equiv base, 3 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 9 mol % ligand **12**, 0.5 M solvent.
[b] Times are reported for complete conversion observed in the amination reaction; h = hours, d = days.
[c] Imine cleavage ranges from 15 min to 4 h under specified conditions; **A:** catalytic transfer hydrogenation; **B**: acidic hydrolysis; **C**: transamination with $NH_2OH{\cdot}HCl$ See Supplementary data for details.
[d] Reported isolated two-step yields are an average of two runs.
[e] 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 6 mol % ligand **12**.
[f] 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 15 mol % ligand **12**.

We have demonstrated the ability to use a Pd-catalyzed amination reaction to convert diverse aryl bromides to their corresponding primary anilines over two steps using benzophenone imine under mild conditions. Particularly, the catalyst system described allows this conversion to proceed at 30 °C using a weak inorganic base, potassium phosphate. The reaction proceeds in a predictable manner with respect to aryl bromide reactivities. Both $Pd_2dba_3{\cdot}CHCl_3$ and ligand **12** are air-stable and commercially available. The reactions were performed in a multireaction block without the need of a glove box or Schlenk techniques. The intermediate imines can be easily converted to the corresponding anilines using procedures described previously.[3a] Work toward Pd-catalyzed aminations of aryl bromides with other ammonia equivalents using ligand **12** is underway and results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2009.01.091.

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17. *Representative procedure: Methyl-4-aminobenzoate* (Table 3, entry 5): A glass reaction vessel part of a multireaction block equipped with a magnetic stir bar was charged with, in order: $Pd_2(dba)_3{\cdot}CHCl_3$ (27 mg, 0.03 mmol), ligand **12** (34 mg, 0.08 mmol), K_3PO_4 (711 mg, 3.25 mmol), methyl-4-bromobenzoate (279 mg, 1.30 mmol), benzophenone imine (0.26 mL, 1.56 mmol), and DME (2.6 mL). The reaction vessel was evacuated and refilled with nitrogen twice. The reaction mixture was stirred at 30 °C under nitrogen. After 28 h, the reaction mixture was cooled to ambient temperature, diluted to 50 mL with diethyl ether, filtered through a pad of Celite, and concentrated in vacuo. The crude ketimine was suspended in 1:1 1N HCl:THF (13 mL) and stirred at room temperature for 3 h. THF was then removed by rotary evaporation and the aqueous residue was washed with 2:1 hexanes:ethyl acetate (50 mL). The layers were separated and the organic layer was extracted with 4 N HCl (100 mL). The pooled aqueous layers were basified to pH 9 using solid $NaHCO_3$. The aqueous layer was then extracted with ethyl acetate (2 × 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (2–90% ethyl acetate:hexanes) to afford methyl-4-aminobenzoate (179 mg, 91%) as a white, crystalline solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.92 (m, 2H), 6.55–6.68 (m, 2H), 4.01(s, 2H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.15, 150.90, 131.48, 119.40, 113.66, 51.50. The spectroscopic data were in excellent agreement with reported values.[5a]
18. The procedure followed for the reaction and work-up was the same for all aryl bromides reported in Table 3 except for Pd and ligand loading. Three different procedures were used for cleavage of the intermediate ketimine, depending on the substrate, as footnoted under Table 3. The procedure **B**, followed above, was used in the cleavage reactions of nine intermediates (Table 3, entries 3–11). Procedure **A** (catalytic transfer hydrogenation) and procedure **C** (transamination with hydroxylamine hydrochloride) used for Table 3, entry 1 and Table 3, entry 2, respectively, are detailed in the Supplementary data. All products are known compounds and were easily identified by comparison of the spectroscopic data with those reported. The purity of all compounds was determined by ^{13}C NMR and LC/MS.
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