One-Pot Synthesis of Symmetrical Di- and Triarylamines Using Urea as the Source of the Amino Group

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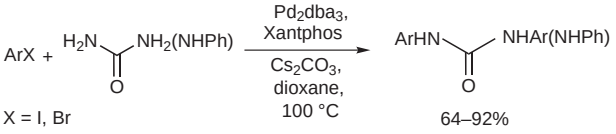
Abstract: A simple one-pot palladium-catalyzed reaction for the conversion of aryl halides to aryl amines using urea as an ammonia equivalent is reported. Arylation of urea in the presence of Pd_2dba_3, *t*-$Bu_3P{\cdot}HBF_4$ and *t*-BuOK in dioxane gives di- and triarylamines in 65–95% yields.

Key words: palladium, arylations, amines, ammonia equivalents, urea

Palladium-catalyzed arylation of amines, the Buchwald–Hartwig reaction, is at present widely used for the synthesis of various secondary and tertiary arylamines.[1] However, such reaction has not yet been carried out with ammonia, and the only procedure allowing one to obtain symmetrical di- and triarylamines in one step directly from aryl halides is the arylation of lithium amide.[2] With *para*- and *meta*-substituted aryl halides it gives triarylamines (75–82%) and with *ortho*-substituted aryl halides diarylamines (64–95%).

Here we describe a new convenient method for the synthesis of symmetrical di- and triarylamines using urea, a cheap and easily accessible reagent, as an ammonia equivalent.

In the previous papers we have developed an efficient method for the synthesis of *N*,*N*-diaryl- and *N*-aryl-*N*′-phenylureas which is based on the reaction of aryl halides with ureas in the presence of Pd_2dba_3, Xantphos and Cs_2CO_3 in dioxane (Equation 1).



Equation 1

However, these conditions allow one to carry out the reaction only with aryl iodides and aryl bromides bearing electron-withdrawing groups (EWG).[3] Modification of Xantphos by CF_3 groups in 3,5-positions of phenyl rings made it possible to use aryl bromides with a broader range of substituents.[4] Nevertheless the modified catalytic system was not efficient for aryl chlorides and electron-rich aryl bromides.

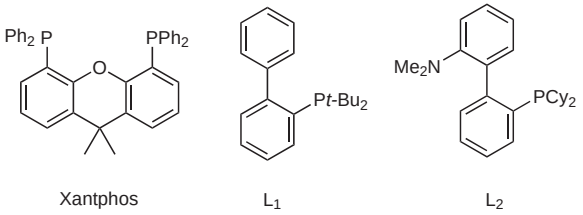


Figure 1

Electron-rich bulky phosphines, L_1, L_2 and *t*-Bu_3P, are widely used as highly efficient ligands in the amination of electron-rich aryl bromides and aryl chlorides.[5,6] We examined the effect of these ligands in the reaction of *p*-bromotoluene with urea, which in the presence of Xantphos and Cs_2CO_3 as a base proceeded to 62% conversion and gave low yield of *N*,*N*′-diarylurea (7%).[3] The couplings were carried out with 2 mol% of Pd_2dba_3 (4 mol% Pd) and 6 mol% of L_1, L_2 or *t*-Bu_3P in dioxane at 100 °C (Table 1). With the same base (Cs_2CO_3) these ligands were even less efficient than Xantphos (entries 1–3), using *t*-BuONa as a

Table 1 Evaluation of Bases and Phosphine Ligands for the Palladium-Catalyzed Reaction of *p*-Bromotoluene with Urea[a]

Entry	Ligand	Base	Reaction time (h)	Conversion of *p*-bromotoluene (%)
1	Cy_3P	Cs_2CO_3	20	0
2	*t*-Bu_3P	Cs_2CO_3	18	9
3	L_1	Cs_2CO_3	18	0
4	L_1	*t*-BuONa	14	31
5	L_2	*t*-BuONa	14	39
6	*t*-Bu_3P	*t*-BuOK	21	100
7	L_1	*t*-BuOK	14	100
8	L_2	*t*-BuOK	14	100

[a] The reactions were carried out with 1.5 mmol of aryl halide, 0.5 mmol of urea, 2 mol% of $Pd_2dba_3{\cdot}CHCl_3$ (4 mol% Pd), 6 mol% of the ligand, 2.1 mmol of the base in 5 mL of dioxane at 100 °C under argon to the point when the conversion of the aryl bromide (as shown by GC) did not increase further.

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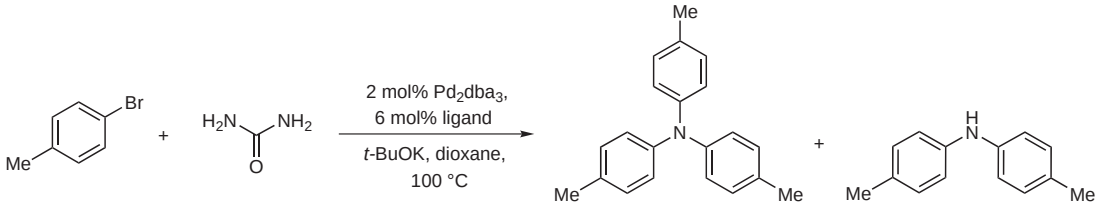
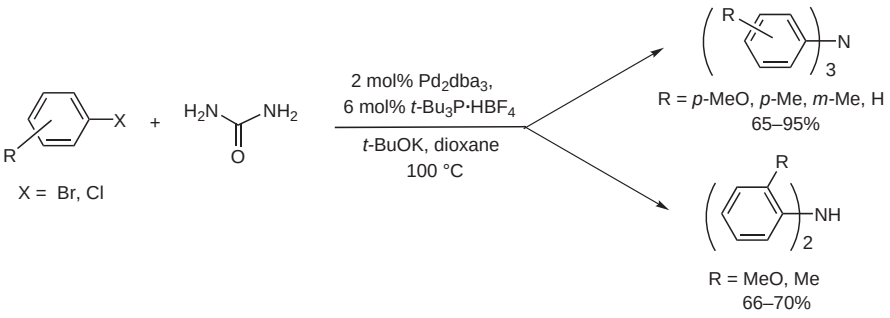


Equation 2

base resulted in somewhat better, but still low, conversion of *p*-bromotoluene (entries 4, 5). Complete consumption of the starting aryl halide was achieved only when electron-rich ligands (L_1, L_2, P*t*-Bu_3) were combined with a strong base *t*-BuOK (entries 6–8). However, the most surprising thing was a complete turn of the reaction course with this new catalytic system: instead of the expected *N*,*N*′-ditolylurea, di- and tritolylamines were formed as the main products (Equation 2).

Examining the reaction products, we found that in the presence of 2-(di-*tert*-butylphosphino)biphenyl L_1 as a ligand (Figure 1) the coupling of *p*-bromotoluene with urea affords the mixture of di- and tri(*p*-tolyl)amines in 32% and 41% yields correspondingly. In contrast, em-

Table 2 Palladium-Catalyzed Synthesis of Di- and Triarylamines from Aryl Halides and Urea[a]



Entry	R	X	Ligand	Reaction time (h)	Conversion of aryl halide (%)	Isolated yield (%)[b]	
						Ar_3N	Ar_2NH
1	*p*-Me	Br	L_1	21	100	32	41
2	*p*-Me	Br	L_2	19	100	73	7
3	*p*-Me	Br	*t*-Bu_3P[c]	18	100	80	–
4	*m*-Me	Br	*t*-Bu_3P	21	100	85	
5	*p*-MeO	Br	*t*-Bu_3P	21	100	65	
6	H	Br	*t*-Bu_3P	19	100	83	
7	*p*-Me	Cl	*t*-Bu_3P	44	85	80	
8	H	Cl	*t*-Bu_3P	20	72	60	5
9	H	Cl	*t*-Bu_3P	46	100	95	Traces
10	*o*-Me	Br	*t*-Bu_3P	8	100		70
11	*o*-MeO	Br	*t*-Bu_3P	20	100		66
12	2,4,6-Me	Cl	*t*-Bu_3P	46	78		60
13[d]	2,4,6-Me	Cl	*t*-Bu_3P	45	90		87

[a] The reactions were carried out in sealed vessels with aryl halide (1.65 mmol), urea (0.5 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (2 mol%, 4 mol% Pd), ligand (6 mol%), *t*-BuOK (2.9 mmol) in dioxane (6 mL) at 100 °C under argon to the point when the conversion of the aryl bromide (as shown by GC) did not increase further.
[b] The calculation of the yields was based on urea, taking into account that the only nitrogen in urea is involved in the reaction.
[c] The ligand was employed as a salt, *t*-$Bu_3P{\cdot}HBF_4$.
[d] 5 mol% of Pd_2dba_3 (10 mol% of Pd) and 15 mol% of the ligand were used.

ployment of L_2 provides selective formation of tri(*p*-tolyl)amine (73%) giving only small amount of di(*p*-tolyl)amine (7%). The best yield of tri(*p*-tolyl)amine (80%) is obtained using *t*-Bu_3P as a ligand (Table 2, entries 1–3).

New conditions (2 mol% of $Pd_2dba_3{\cdot}CHCl_3$, 6 mol% of *t*-$Bu_3P{\cdot}HBF_4$, *t*-BuOK, dioxane) were applied for the synthesis of various triarylamines from unactivated aryl halides and urea.[7] The data presented in Table 2 show that under optimized conditions the reactions of several aryl halides bearing electron-donating substituents in *meta*- and *para*-positions afford triarylamines in high yields. It should be noted that *t*-Bu_3P can be used as a salt *t*-$Bu_3P{\cdot}HBF_4$, which, in contrast to free phosphine, is an air-stable solid.[8] Amination of bromobenzene, *para*- and *meta*-bromotoluenes results in 80–85% yields of triarylamines (entries 3, 4, 6), however, in the reaction with less active *p*-bromoanisole a moderate yield is observed (65%, entry 5).

We have shown that aryl chlorides, including non-activated, also can be aminated under these conditions. In the reactions of urea with chlorobenzene and *p*-chlorotoluene the yields of triarylamines reach 80–95% (entries 7–9). It is worth noting that coupling reactions with aryl chlorides proceed considerably slower than the reactions with aryl bromides, giving, however, comparable or even higher product yields (compare entries 3, 7 and 6, 9).

The reactivity of *ortho*-substituted aryl halides differs markedly from that of *meta*- and *para*-substituted aryl halides: coupling of *ortho*-bromotoluene and *ortho*-bromoanisole with urea selectively forms diarylamines in 66–70% yield (Table 2, entries 10, 11). Even chloromesitylene, aryl chloride having two substituents in *ortho*-positions, was found to be a suitable substrate for amination (entries 12, 13, Equation 3).

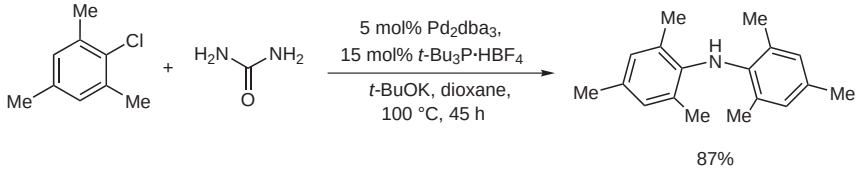
Obviously, the subsequent arylation of *ortho*-substituted diarylamines under these conditions is hampered due to steric hindrance, and triarylamines bearing *ortho*-substituents in each phenyl group cannot be obtained via amination of aryl halides under these conditions. A similar situation was observed in the palladium-catalyzed arylation of lithium amide, where *ortho*-substituted aryl halides gave only diarylamines, while *para* and *meta* isomers gave triarylamines.[2]

Moreover, double arylation of anilines in the presence Pd_2dba_3/L_1 allows the production of triarylamines containing only one *ortho* substituent.[9]

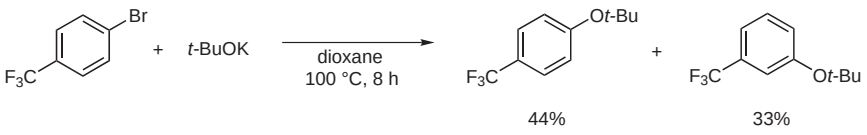
The scope of the described reaction is limited to aryl halides without an electron-withdrawing group. In case of activated aryl halides the corresponding aryl-*tert*-butyl ethers were formed as the main products. For example, our attempt of coupling of *para*-bromobenzotrifluoride with urea resulted in a mixture of *para*- and *meta*-trifluoromethylphenyl-*tert*-butyl ethers in 77% overall yield. Similar result was obtained in a noncatalytic reaction. It is evident that reaction with electron-poor aryl bromide proceeds through aryne mechanism of nucleophilic substitution, where *t*-BuOK acts both as a base and a nucleophile (Equation 4).

Two pathways can be proposed for the formation of di- and triarylamines in the reaction of urea with aryl halides. The first one begins with the arylation of urea, followed by cleavage of resultant arylurea to carbamate and aniline, which subsequently undergoes arylation to give di- or triarylamines (Scheme 1).

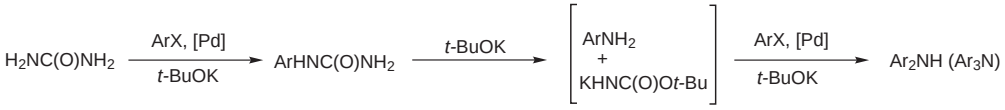
But the catalytic system employed, Pd_2dba_3–L_1–*t*-BuOK, was shown to be inefficient for the arylation of amides: we observed only traces of N-arylated amide (<2%) in the coupling of *p*-bromotoluene with *p*-methylbenzamide during 19 hours at 100 °C. Therefore, as more probable we consider the second pathway with the initial dissociation of urea to ammonia, and subsequent arylation of ammonia or potassium amide (Scheme 2).



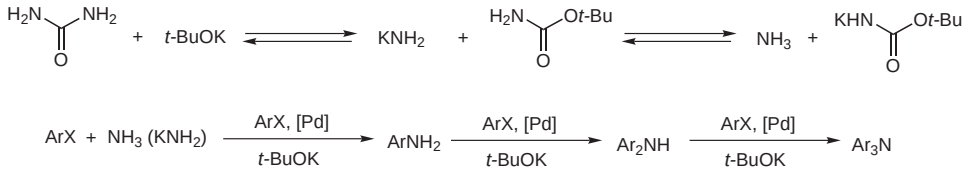
Equation 3



Equation 4



Scheme 1



Scheme 2

Ligands L_1 and L_2 are known to be very effective for palladium-catalyzed arylation of amines, even at room temperature[5] and, as it was mentioned previously, have been used for the arylation of lithium amide.[2] It is also worth pointing out that in aqueous alkali urea acts as ammonia source giving trialkylamines in the reactions with alkyl, allyl and benzylchlorides.[10]

In summary, a new method for the one-pot preparation of arylamines from aryl halides and urea is reported. Arylation of urea in the presence of Pd_2dba_3, P*t*-Bu_3 and *t*-BuOK gives triarylamines with *para*- and *meta*-substituted aryl halides and diarylamines with *ortho*-substituted substrates.

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(7) **Representative Procedure for Tri(*m*-tolyl)amine.** *m*-Bromotoluene (282 mg, 1.65 mmol), urea (31 mg, 0.51 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (31.5 mg, 0.03 mmol), *t*-$Bu_3P{\cdot}HBF_4$ (25.2 mg, 0.087 mmol), *t*-BuOK (325 mg, 2.9 mmol), and anhydrous dioxane (6 mL) purged with argon were placed into an argon-filled reactor. The reaction was carried out with stirring at 100 °C under positive argon pressure. After the aryl halide was completely consumed (according to GC), the reaction mixture was cooled to r.t., diluted with EtOAc (30 mL), filtered through the short plug of Celite® and evaporated on silica gel. The residue was chromatographed on silica gel (Merck 60, 40–63 μm), eluting with light PE, then EtOAc–light PE mixture 1:40 and 1:20 at the end to give 122 mg (85%) of the product as a white solid. Mp 66 °C (ref. 2: 64–65 °C). ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.14 (t, 3 H, 7.7 Hz), 6.77–6.87 (m, 9 H), 2.23 (s, 9 H). MS (EI, 70 eV): *m/z* (%) = 287 (100) [M^+], 271 (2) [$M - CH_3 - H^+$], 257 (4) [$M^+ - 2\ CH_3$], 180 (5) [$C_{13}H_{10}N^+$].

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