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Palladium-catalyzed reaction of aryl halides with ureas

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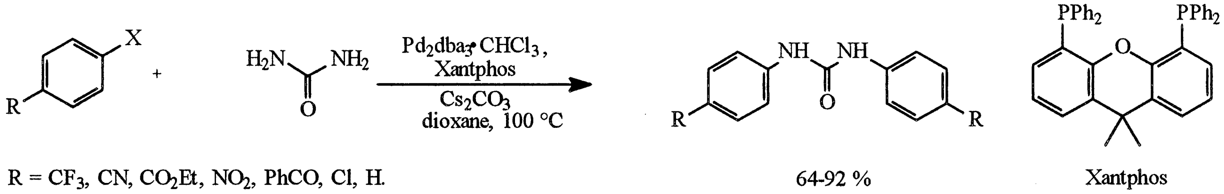
Abstract—A new method for the palladium-catalyzed arylation of ureas is described. The coupling reaction of urea and phenylurea with aryl halides containing electron-withdrawing groups in the *p*-position in dioxane in the presence of 0.5–1.0 mol% of $Pd_2dba_3{\cdot}CHCl_3$, Xantphos and Cs_2CO_3 as a base gives *N*,*N*′-diarylureas in yields of 64–92%. © 2001 Elsevier Science Ltd. All rights reserved.

N,*N*′-Diarylureas are valuable starting materials for organic synthesis; they have also found numerous applications as drugs, pesticides, herbicides, antioxidants[1,2] and anion binding receptors.[3] Standard methods for the synthesis of diarylureas involve highly toxic reagents, such as isocyanates, phosgene and carbon monoxide.[1,2] The recent progress in palladium-catalyzed amination reactions has opened synthetic routes to a wide range of arylamine containing various functional groups.[4] However, it was only recently that the group of Buchwald successfully carried out the intermolecular arylation of amides,[5] though a few isolated examples of intramolecular amidation had been described earlier.[6] Several cases of carbamate[7] and lactam[8] arylation have also been described. As to the catalytic reaction of arylation of ureas, which is of considerable interest for organic synthesis, no such investigations have been reported.

Here, we report a simple catalytic method for the conversion of aryl halides to diarylureas. In order to find a proper ligand we examined a number of phosphines ($P(o\text{-}Tol)_3$, DPPF, DPE-Phos, Xantphos) in the reaction of *p*-bromotrifluoromethylbenzene with urea (1:2 mol ratio) in dioxane at 100°C in the presence of 1 mol% of $Pd_2dba_3{\cdot}CHCl_3$ and 3 mol% of phosphine using Cs_2CO_3 as a base. However, only Xantphos was found to promote an effective coupling reaction (Scheme 1, Table 1). We have carried out a series of urea arylation reactions with different aryl halides in the presence of this ligand.

As shown in Table 1 (entries 1–5) the arylation of urea with aryl halides having electron-withdrawing substituents in the *p*-position readily goes with 1–2 mol% of the catalyst and produces *N*,*N*′-diarylureas in high yields (75–92%), and even with a two-fold excess of urea (entry 1) only a small amount of monoarylurea is formed. However, the reactions with unactivated and slightly activated aryl halides requires higher catalyst quantities for the complete conversion of the starting aryl halides and give lower yields of desired products (entries 6–8). In some cases (entries 6 and 9) we observed formation of substantial amounts of *N*-phenylation products arising from aryl group exchange between the aryl group bound to palladium and the phenyl group of Xantphos.[9] This side process becomes even more evident in the reactions of aryl halides containing electron-donor substituents. Thus, even in the presence of 4 mol% catalyst the reaction of 4-bromo-



Scheme 1.

Keywords: palladium and compounds; catalysis; aryl halides; arylation; ureas.

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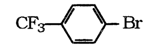
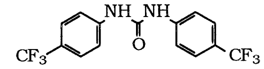
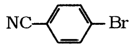
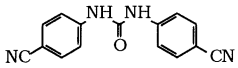
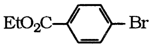
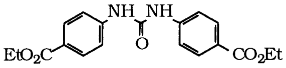
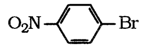
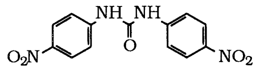
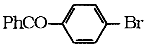
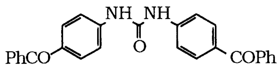
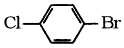
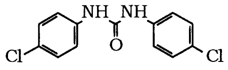
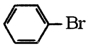
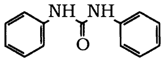
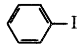
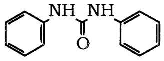
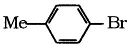
Table 1. Palladium-catalyzed synthesis of symmetrical *N*,*N*′-diarylureasm42^{a}

Entry	Aryl halide	Mol % Pd	Reaction time, h	Reaction product	Yield, %^{b}
1		2	4		89^{c}
2		1	6.5		92^{d}
3		1	4		86
4		1	4		75
5		1	2.5		89^{e}
6		4	10		64^{f}
7		4	10		70
8		4	13		74
9		4	20	$C_6H_5NHC(O)NHC_6H_5$ + p-$MeC_6H_4NHC(O)NHC_6H_5$ + p-$MeC_6H_4NHC(O)NHC_6H_4Me$-p	-^{g}

(a) The reactions were carried out with 1 mmol of aryl halide, 0.65 mmol of urea, 0.5-2 mol % of $Pd_2dba_3{\cdot}CHCl_3$ (1-4 mol % Pd), 1.5 - 6 mol % Xantphos, 1.4 mmol Cs_2CO_3 in 4 ml of dioxane at 100°C under argon to complete consumption of the starting aryl halide (as shown by GC or TLC).

(b) Presented in the Table are the yields of pure isolated compounds, purified by column chromatography on silica gel 40-100 μm. All of the substances were characterised by ^{1}H NMR and IR spectra .

(c) 2 mmol of urea was used.

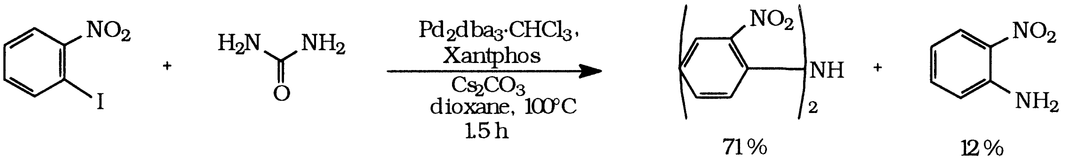
(d) The reaction was carried out at 85°C.

(e) The product was purified by the precipitation from DMF solution with water.

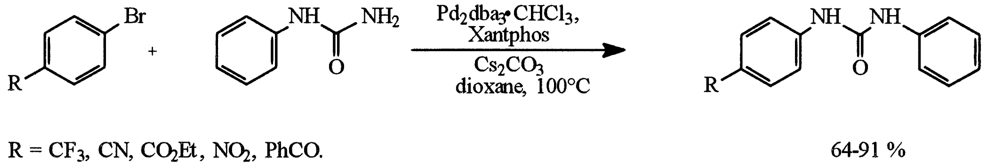
(f) The yield after recrystallisation from ethyl alcohol. After column chromatography the product was contaminated with ~14% of *N*-phenyl-*N'*-(*p*-chlorophenyl)urea (according to ^{1}H NMR and MS data).

(g) The reaction stopped at 62% of conversion. The product was obtained in 22% overall yield and was a mixture of *N, N'*-di-(*p*-tolyl)urea, *N*-(*p*-tolyl)-*N'*-phenylurea and *N, N'*-diphenylurea in the molar ratio 1.30 : 1.93: 1.00 (as shown by ^{1}H NMR and MS spectra).

toluene with urea proceeds to 62% conversion and gives a mixture of *N*,*N*′-di-(*p*-tolyl)urea, *N*-(*p*-tolyl)-*N*′-phenylurea and *N*,*N*′-diphenylurea (entry 9) in low overall yield (22%). We also isolated the corresponding diarylamines (12–14%) as side products in entries 6–8. Formation of diarylamines may be explained by the arylation of the corresponding aniline, resulting from the dissociation of *N*,*N*′-diarylurea to aniline and arylisocyanate.[10] It is worth noting that formation of diarylamines instead of *N*,*N*′-diarylureas becomes a dominant pathway in the reaction of 2-nitroiodobenzene (Scheme 2).

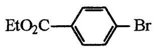
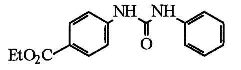
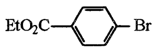
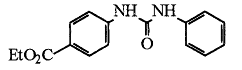
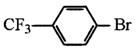
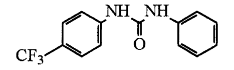
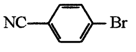
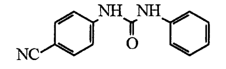
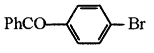
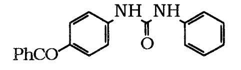
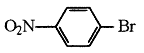
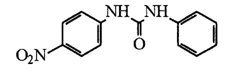


Scheme 2.



Scheme 3.

Table 2. Palladium-catalyzed synthesis of *N*-aryl-*N*′-phenylureas[a]

Entry	Aryl halide	Mol % Pd	Reaction time, h	Reaction product	Yield, %[b]
1		0.5	4		58
2		2	1		91
3		2	1		90
4		2	1		80
5		2	1.5		87
6		2	1		64

(a) The reactions were carried out with 0.60 mmol of aryl halide, 0.60 mmol of phenylurea, 0.25-1 mol % of $Pd_2dba_3 \cdot CHCl_3$ (0.5-2 mol % Pd), 0.75-3 mol % Xantphos, 0.84 mmol Cs_2CO_3 in 3 ml of dioxane at 100°C under argon to complete consumption of the starting phenylurea (as shown by TLC).

(b) Presented in the Table are the yields of pure isolated compounds, purified by column chromatography on silica gel 40-100 μm. All of the substances were characterised by ^{1}H NMR and IR spectra.

We have also shown that various *N*-aryl-*N*′-phenylureas can be obtained in high yields using *N*-phenylurea and activated aryl bromides as starting reagents[11] (Scheme 3). The results are given in Table 2.

The reaction is accompanied by the disproportionation of the product giving *N*,*N*′-diaryl- and *N*,*N*′-diphenylurea. The control experiment carried out in the presence of Cs_2CO_3 showed that the disproportionation of *N*-aryl-*N*′-phenylurea takes place in the absence of the catalyst.[12] To minimize the disproportionation process, the amount of the catalyst was increased from 0.5 to 2 mol% resulting in a decrease of reaction time and substantially improved yields (entries 2–6). The only exception was the reaction of 4-nitrobromobenzene, which besides *N*-4-nitrophenyl-*N*′-phenylurea gave a substantial amount of side products: *N*,*N*′-diphenylurea, bis-(4-nitrophenyl)amine and 4-nitrophenylphenylamine.

In summary, we developed an efficient method for the synthesis of *N*,*N*′-diarylureas and *N*-aryl-*N*′-phenylureas by the reaction of *p*-substituted activated aryl bromides with urea and phenylurea under Pd-catalysis. The method allows us to obtain both symmetrical and unsymmetrical *N*,*N*′-diarylureas in high yields.

Acknowledgements

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9. The exchange of aryl groups between phosphine and aryl halide was observed, though in a lesser degree, in the amidation reaction of unactivated aryl halides, see: Ref. 5.
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11. Representative procedure, *N*-(*p*-carboethoxyphenyl)-*N*′-phenylurea: 143 mg ethyl-*p*-bromobenzoate (0.62 mmol), 81 mg of phenylurea (0.60 mmol), 6.3 mg of $Pd_2dba_3 \cdot CHCl_3$ (6.1×10^{-3} mmol), 11.0 mg of Xantphos (19.0×10^{-3} mmol), 280 mg of dried Cs_2CO_3 (0.859 mmol) and 3 ml of dioxane purged with argon were placed into the argon filled reactor. The reaction mixture was degassed by several freeze–pump–thaw cycles and the reactor was filled with argon. The reaction was carried out with stirring at 100°C under positive argon pressure. After 1 h, TLC showed the absence of the starting phenylurea. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (40 ml), filtered and evaporated to dryness. The residue was chromatographed on silica gel 40–100 μm, eluting with a 1:2 ethyl acetate:light petroleum ether mixture (v/v), to give 156 mg (91%) of white solid: mp 168–170°C (lit. mp 169°C,[13] 163°C[14]).
12. The heating of *N*-(*p*-carboethoxyphenyl)-*N*′-phenylurea in dioxane at 100°C with Cs_2CO_3 during 2 h yields ~10% of *N*,*N*′-diphenyl- and ~10% of *N*,*N*′-bis(4-carboethoxyphenyl)urea (according to ^1H NMR data).
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