Solvent-free Pd-catalysed N-arylation of amines, amides and diaza-18-crown-6

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The N-arylation of amines, amides and diaza-18-crown-6 with weakly activated aryl bromides catalysed by Pd^0/L and the arylation of pyrrolidone-2 with 2-bromothiophene catalysed by CuI/1,2-di(methylamino)cyclohexane can be performed in the presence of graphite at 60–100 °C without solvent to give arylation products in good yields (60–78%).

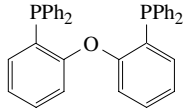
One of the greatest achievements in organometallic chemistry is the development of new synthetic approaches to organic compounds with new C_{sp^2}–C and C_{sp^2}–heteroatom bonds based upon transition metal catalysis. A special place among these reactions belongs to the formation of C_{sp^2}–N bonds according to Buchwald and Hartwig.[1,2] These reactions usually require the presence of a strong base, Bu^tONa or Cs_2CO_3, and are catalysed by palladium[1,2] or nickel[2] complexes in such solvents as toluene and dioxane.

The main trend in modern organic chemistry is the development of clean technologies, including the attempts to avoid toxic, volatile and flammable solvents, which are extensively used in conventional organic synthesis. For this purpose, reactions are carried out in environment-friendly media such as water,[3] $sqCO_2$[4] and ionic liquids.[5]

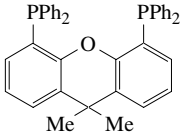
Transition metal catalysed reactions in a solid phase are also of paramount importance. However, the use of solid supported transition metal catalysts[6] is often described as 'solid-state chemistry', although there is a principal difference between this approach and actually performed reactions in a solid phase.[7]

In this communication we present the examples of transition metal catalysed reactions performed in a solid phase of graphite under mechanical impact. A few solvent-free Pd-catalysed amination reactions have been reported.[8] However, they were performed using liquid reagents and stoichiometric amounts of Bu^tONa as a base, which generated liquid Bu^tOH in the course of reaction. In contrast, we used solid reagents and Cs_2CO_3 (1.5 mmol per mmol of substrate) as a base. The addition of graphite is necessary to prevent the caking of the reaction mixture, which solidified after stirring for 10–15 min at 100 °C.

We studied the arylation reactions of various amines, including diaza-18-crown-6, benzamide and urea, *i.e.*, weakly basic nitrogen compounds, because these reactions are most difficult to perform.[9,10] The reactions were usually carried out at 100 °C under argon for 3–10 h; $Pd(OAc)_2$ and $Pd_2(dba)_3$ were used as pre-catalysts and Xantphos and DPE-phos, as ligands.† The results are summarized in Table 1.

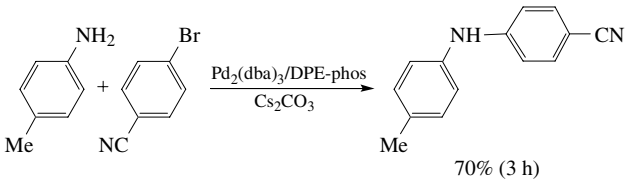


DPE-phos



Xantphos

† *General procedure:* The reaction was performed in a vessel, which consisted of an all-welded steel sphere (d = 25–30 mm) fitted with a steel screw top with a Teflon padding. This vessel was evacuated with the help of a similar screw top, to which a steel tube was welded (d = 4 mm). 0.5 mmol of an NH compound, 0.5 mmol or 1 mmol (depending on the number of NH groups) of aryl bromide, 1 mol% $Pd_2(dba)_3 \cdot CHCl_3$ or 2 mol% $Pd(OAc)_2$, 3 mol% ligand, 1.5 mmol of a base (Cs_2CO_3 or Bu^tONa), 200–300 mg of graphite (Carbopack C, surface area of 10 $m^2\ g^{-1}$) and five steel beads (d = 4 mm) were placed in this vessel. The reaction vessel was evacuated, filled with argon and shaken on a vibrator at 100 °C. The reaction was followed by TLC (on Silufol UV-254 plates) or/and GLC. After the reaction was complete, the reaction mixture was transferred to a SiO_2 column or extracted with ethyl acetate or acetone. The extract was evaporated and the residue was subjected to column chromatography on SiO_2.



Scheme 1

Anilines are the easiest to arylate under these conditions. *p*-Toluidine, for example, reacts with *p*-bromocyanobenzene to form the corresponding diarylamine in 70% yield in 3 h (Table 1, entry 7). This may be compared to 80% yield of the same diarylamine obtained in toluene in the presence of Pd_2dba_3/BINAP (26 h, 100 °C).[11]

The arylation of a less basic aniline, 3-nitro-5-tiophenylaniline, also proceeds without any difficulties and gives a similar yield of the product (entry 8).

In toluene, this reaction afforded the product in 87% yield in 3–4 h (110 °C).[12]

The arylation of diaza-18-crown-6 is of special interest since aza-crown derivatives have found numerous applications.[13] The synthesis of *N*,*N*′-diarylaza-crown ethers is usually a complex and multistage procedure.[14] In this case, arylation methods based on transition metal catalysis are promising.

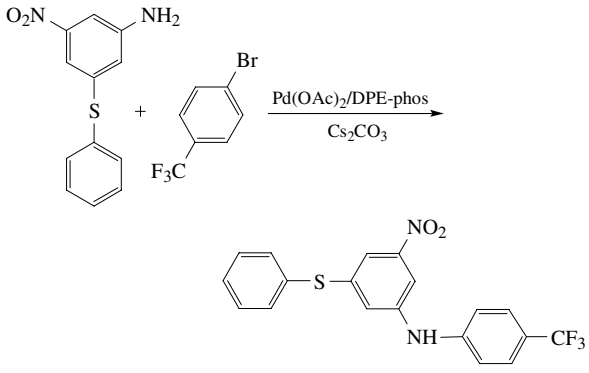
In our conditions with two equivalents of aryl bromide, we have obtained bis[*N*,*N*′-(*p*-trifluoromethylphenyl)]diaza-18-crown-6 in 70% yield (entry 6).

Note that in a toluene solution a monoaza-crown ether was arylated with *p*-bromobenzotrifluoride in the Pd_2dba_3/2-dimethylamino-2′-(dicyclohexylphosphino)biphenyl–Bu^tONa system (80 °C) to give the product in 80% yield in 24 h.[15]

As mentioned above, amides are more difficult to arylate than amines. However, Buchwald found conditions for the arylation of amides, sulfamides, carbamates and lactams;[10] the use of the ligand Xantphos was of key importance.

Under conditions of our experiments, *p*-tolyic acid amide was arylated with *p*-bromocyanobenzene to give a 60% yield of the product in 10 h‡ (entry 5).

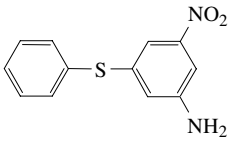
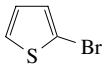
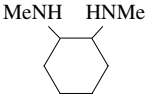
Earlier, we successfully arylated urea with activated aryl bromides in dioxane solutions using the $Pd_2(dba)_3$/Xantphos –



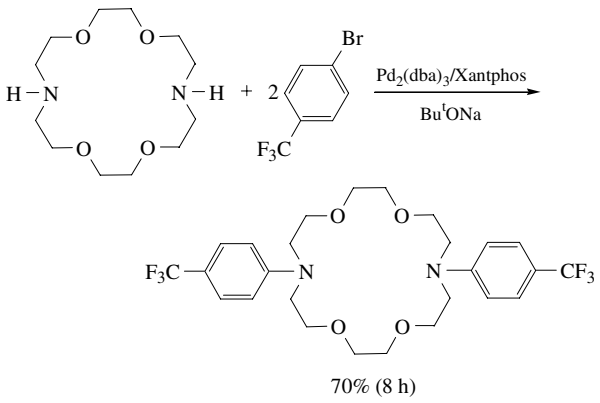
72% (4 h)

Scheme 2

Table 1 Arylation conditions and product yields (100 °C, graphite[a]).

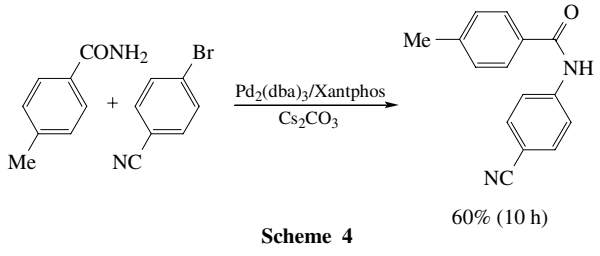
Entry	Substrate	Aryl halide	Pre-catalyst	Ligand	Time/h	Conversion (%)	Yield (%)[b]
1	NH_2CONH_2	*p*-NCC_6H_4Br	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	6	86	65 (75)
2	NH_2CONH_2	*p*-$F_3CC_6H_4Br$	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	5	80	75 (95)
3	NH_2CONH_2	*p*-$O_2NC_6H_4Br$	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	6	85	33 (42)
4	NH_2CONH_2	*p*-$O_2NC_6H_4Br$	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	6	82	68 (80)[c]
5	*p*-$MeC_6H_4CONH_2$	*p*-NCC_6H_4Br	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	10	70	60 (68)
6	Diaza-18-crown-6	*p*-$F_3CC_6H_4Br$	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	8	94	70 (75)
7	*p*-$MeC_6H_4NH_2$	*p*-NCC_6H_4Br	$Pd_2(dba)_3{\cdot}CHCl_3$	DPE-phos	3	78	70 (75)
8		*p*-$F_3CC_6H_4Br$	$Pd(OAc)_2$	DPE-phos	4	83	72 (77)
9			CuI		18	100	78

[a]Typically, we used 0.5 mmol of an NH compound, 0.5–1 mmol of ArBr, 1 mol% $Pd_2(dba)_3$ or 2 mol% $Pd(OAc)_2$, 3 mol% of a ligand and 1.5 mmol of a base. The amount of graphite (Carbopack C, surface area of 10 $m^2\ g^{-1}$) added was 200–300 mg. [b]The yields in parentheses were calculated relative to the amount of the aryl halide actually consumed in the reaction. [c]60 °C.



70% (8 h)

Scheme 3

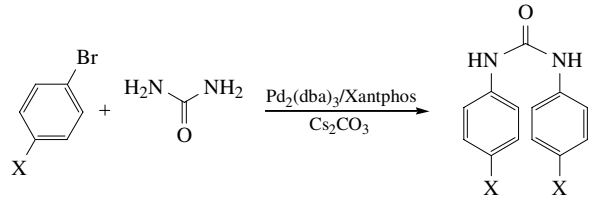


60% (10 h)

Scheme 4

Cs_2CO_3 catalytic system at 100 °C.[9] These reactions can also be easily performed without solvent (entries 1,2).

Urea was arylated with *p*-bromonitrobenzene under these conditions (100 °C); this reaction gave a mixture of products,



X = CF_3, 75%, 5 h [in dioxane 89% (100 °C, 4 h)[9]]

X = CN, 65%, 6 h [in dioxane 92% (100 °C, 6.5 h)[9]]

Scheme 5

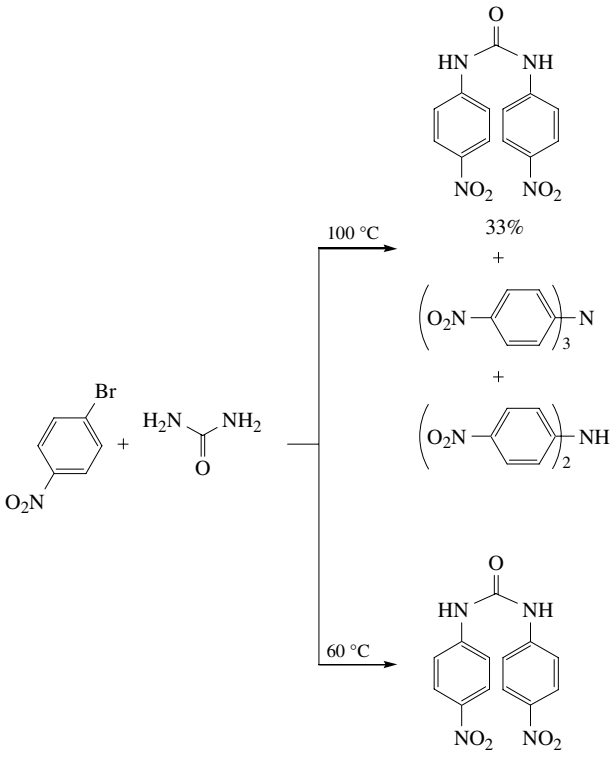
‡ According to ref. 10, the arylation of benzamide with *p*-bromocyanobenzene in dioxane in the $Pd(OAc)_2$/Xantphos–Cs_2CO_3 system gives the product in 93% yield (19 h) at 45 °C.

which contained di- and triarylamines, which resulted from the cleavage of diarylurea followed by arylation. On lowering the temperature to 60 °C, diarylurea became the principal reaction product (entries 3,4).

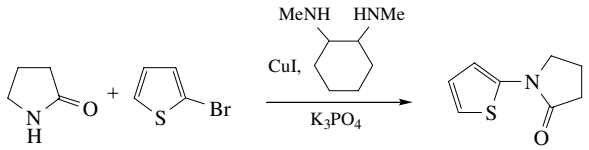
It is well known that the arylation of amides with aryl halides can be performed using catalysis with copper or its derivatives (the Ullmann-Goldberg reaction).[16] Copper chelating additives such as 1,10-phenanthroline allow one to arylate these amides under much milder conditions. *trans*-1,2-Diaminocyclohexane and *trans*-1,2-di(methylamino)cyclohexane are the most effective ligands for the arylation of amides in the presence of copper.[17]

We also carried out the arylation of 2-pyrrolidone with 2-bromothiophene without solvent catalysed by copper iodide (10 mol%) (entry 9).§

In the same system in dioxane, the product was obtained in 96% yield (110 °C, 15–24 h).[17]



Scheme 6



78% (18 h)

Scheme 7

Note that in the majority of the above reactions (entries 1, 3–5, 7), all five components were solids.

All the compounds were characterised by their melting points and ^{1}H NMR spectra, which were consistent with published data.

In summary, we found that the arylation reactions of amines, amides and an aza-crown ether can be performed in a solid phase without solvent to give products in preparative yields.

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§ The reaction catalysed by CuI was carried out in the above vessel using the following amounts of reagents: 1 mmol of 2-pyrrolidone, 1 mmol of 2-bromothiophene, 0.1 mmol of CuI, 0.1 mmol of *trans*-1,2-di(methylamino)cyclohexane, 2 mmol of K_3PO_4 and 300 mg of graphite.

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