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First Palladium-Catalyzed Aminations of Aryl Chlorides[1]

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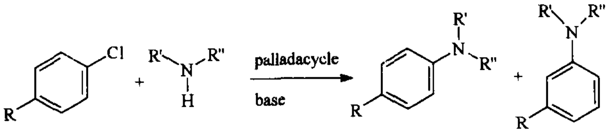
Abstract: *The palladium-catalyzed coupling reaction of aryl chlorides with various amines has been studied for the first time. Crucial for the success of this C-N bond forming reaction is the use of potassium tert-butoxide as base. Turn over numbers up to 900 and yields up to 80 % have been obtained.*

The synthesis of substituted anilines *via* palladium-catalyzed aminations of aryl halides has become an actual subject of study[2]. Unfortunately, only aryl bromides and aryl iodides have been reported to undergo aminations so far[3]. Clearly, an extension of the methodology towards chloroarenes as starting materials would be of high interest due to their availability and low cost. However C-Cl activation is difficult. Recently, we developed an efficient catalyst system for the olefination of aryl chlorides by means of new palladium catalysts e.g. *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (palladacycle) and additional bromide ions as co-catalysts[4]. In order to test our catalyst system for aminations of chloroarenes we studied the coupling reaction of 4-chlorobenzotrifluoride with piperidine as model reaction. Following standard conditions developed by Buchwald[2a] and Hartwig[2c] (toluene, NaO^{t}Bu, 1 mol% palladium catalyst; 100 °C; 24 h) *no conversion at all* was observed. However, a 55 % yield of amination products was realized when the reaction was performed at higher temperatures (> 135 °C) in the presence of 1 mol% palladium catalyst, 0.2 equivalents of LiBr and potassium *tert*-butoxide as base. With slightly higher amounts of amine and base the yield was improved to 74 % (Table, entry 1). Much to our surprise additionally the *meta*-regioisomer was obtained in 9 % yield. This finding can be explained by aryne intermediates which probably form under reaction conditions and which generally display a low regioselectivity[5].

Table. Palladium-Catalyzed Amination of Aryl Chlorides



Entry	R	Amine	Base	Catalyst (mol%)	Co-Catalyst (eq. LiBr)	Yield (%)	Selectivity (para : meta)
1	CF_3	2.3 eq. Piperidine	2.0 eq. KO^tBu	1	0.2	74[a]	7 : 1
2	CF_3	2.3 eq. Piperidine	2.0 eq. KO^tBu	-	0.2	79[a]	1 : 1
3	CF_3	2.3 eq. Piperidine	2.0 eq. KO^tBu	0.1	0.2	98[b]	13 : 1
4	CF_3	2.0 eq. Di-n-butylamine	2.0 eq. KO^tBu	1	0.2	60[c]	10 : 1
5	CF_3	2.0 eq. *N*-Methylaniline	2.0 eq. KO^tBu	1	0.2	60[a]	20 : 1
6	CF_3	1.2 eq. Morpholine	1.4 eq. KO^tBu	1	0.2	58[a]	17 : 1
7	COPh	2.3 eq. Piperidine	2.0 eq. KO^tBu	1	0.2	40[a]	> 50 : 1
8	COPh	2.3 eq. Piperidine	2.0 eq. KO^tBu	-	0.2	< 5[c]	-

[a] Isolated yields; [b] determined by GC with hexadecane as internal standard; [c] determined by GC on the basis of area percentage.

Indeed, performing the reaction without any catalyst yielded a 1 : 1 mixture of the *para-* and *meta-*product in 79% yield (entry 2). Addition of LiBr slightly improves the activity of the palladium catalyst resulting in more selective product distribution. With lithium and sodium *tert*-butoxide just low conversions (< 10 %) have been obtained in contrast to previous results$^{2)}$. Interestingly, the catalyst system displays similar good activity even if lower concentrations (0.1 mol%) palladium were used (entry 3). To evaluate the scope of the reaction, a series of various amines and aryl chlorides was subjected to the optimized reaction conditions$^{6)}$. Both secondary aryl- and alkylamines provide the corresponding anilines in good yield. Aryl chlorides with electron-withdrawing substituents reacted selectively.

Concerning the mechanism we believe that the catalytically active species is formed by reduction of the palladacycle$^{7)}$. The resulting Pd(0)-complex either undergoes an oxidative addition with the aryl chloride or is directly involved in an aryne type mechanism. Both reaction pathways seem possible and might run at the same time. Further work to elaborate the mechanism is in progress. In summary, this work constitutes the first example of a palladium-catalyzed amination of aryl chlorides. The new reaction protocol expands the scope of the method.

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References and Notes

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6. Typical reaction: 0.27 ml 4-chlorobenzotrifluoride (**1**), 0.46 ml piperidine (**2**), 0.45 g potassium *tert*-butoxide, 35 mg LiBr and 9.4 mg *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) were heated for 24 h in 10 ml toluene. The reaction is performed at 135 - 140°C in an Ace pressure tube purchased by Aldrich. After cooling, the reaction mixture was filtered and the solvent was removed *in vacuo*. Isolation of pure product as a slightly yellow oil was accomplished by chromatography on silica gel (50/1 hexane/ethyl acetate) (0.34 g, 74 %).
   ^{1}H NMR ($CDCl_3$, 360.13 MHz) δ (ppm) 1.64 (m, 6H), 3.25 (t, J = 4.8 Hz, 4H), 6.90 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ (ppm) 24.3, 25.4, 49.3, 114.6, 119.2 (q, J = 32.8 Hz), 126.3 (q, J = 3.6 Hz),153.8.
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