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Palladium-Catalyzed Synthesis of Aryl-Substituted Polyamine Compounds from Aryl Halides.

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Abstract: The reaction of polyamines having primary amino groups and 1,2-diaminoethane and/or 1,3-diaminopropane fragments with aryl bromides or iodides in the presence of sodium *tert*-butoxide and (dppf)PdCl$_2$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) proceeds selectively leading to monoaryl-substituted derivatives of polyamine. This reaction provides a convenient method of arylation of di-, tri- and tetraamine compounds. The Pd-catalyzed reactions of 1,3-diaminopropane and 3,3'-diaminodipropylamine with more reactive 1-bromonaphthalene can be used for the preparation of *sym*-dinaphthyl derivatives of these amines.

Several recent papers are devoted to the study of the reactivity 1,2-diaminoethane, 1,3-diaminopropane and polyamine derivatives. The growing interest is related to the wide use of these compounds in areas such as pharmacology[1] and coordination chemistry[2]. In spite of the explosive proliferation of research works on the polyamines since the early 1970s, most of these investigations are directed to their synthesis. Although a large number of synthetic methods for the preparation of aromatic amines have been reported[3], general techniques for the synthesis of aryl-substituted polyamines are still of great interest. The recent intensive works of Buchwald's[4] and Hartwig's[5] groups followed the preliminary communications of Migita and co-workers[6], have developed Pd-catalyzed arylation of $R_3SnNR'_2$ and a variety of primary and secondary amines. In the last case this reaction proceeds with the presence of different palladium catalyst-precursors having phosphine ligands and t-BuONa as base. The Pd-catalyzed arylation of polyamine compounds would provide an interesting approach for the synthesis of aryl-substituted derivatives of polyamines when chelating properties of polyamines do not prevent the catalytic cycle of the carbon-nitrogen bond formation[7]. We report here the successful arylation of polyamines having primary amino groups and 1,2-diaminoethane or 1,3-diaminopropane substructures.

1,3-Diaminopropane was reacted with a variety of substituted aryl bromides and iodides by using sodium *tert*-butoxide as base[8] and (dppf)PdCl$_2$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) as catalyst (Equation 1). In a typical experimental procedure a mixture of aryl halide (1 equiv), 1,3-diaminopropane (3 equiv), t-BuONa (2 equiv), Pd-catalyst (0.5-1 mol %) and dppf (1-2 mol %)[9] was refluxed in dioxane under an argon atmosphere[10]. The obtained results are summarized in Table 1.

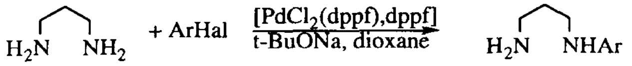

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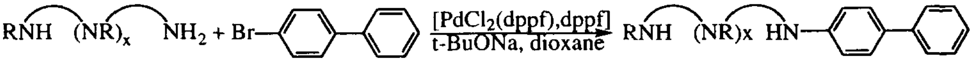
Table 1. Palladium-Catalyzed Reactions of Aryl Halides with 1,3-Diaminopropane[a]

Entry	Aryl halide	Product	Time, h	Yield, %[b]
1.	C_6H_5Br	$C_6H_5NHCH_2CH_2CH_2NH_2$	100	70
2.	C_6H_5I	$C_6H_5NHCH_2CH_2CH_2NH_2$	100	68
3.	$C_6H_5C_6H_4Br$	$C_6H_5C_6H_4NHCH_2CH_2CH_2NH_2$	24	75
4.	*p*-(*p*-$ClC_6H_4CO)C_6H_4Br$	*p*-(*p*-$ClC_6H_4CO)C_6H_4NHCH_2CH_2CH_2NH_2$	2	77
5.	*p*-$CF_3C_6H_4Br$	*p*-$CF_3C_6H_4NHCH_2CH_2CH_2NH_2$	24	53
6.	*p*-$CH_3COC_6H_4Br$	*p*-$CH_3COC_6H_4NHCH_2CH_2CH_2NH_2$	4	21
7.	*p*-$CH_3C_6H_4I$	*p*-$CH_3C_6H_4NHCH_2CH_2CH_2NH_2$	24	49
8.	*o*-$CH_3OC_6H_4Br$	*o*-$CH_3OC_6H_4NHCH_2CH_2CH_2NH_2$	100	20[c]
9.	*p*-$CH_3OC_6H_4Br$	*p*-$CH_3OC_6H_4NHCH_2CH_2CH_2NH_2$	100	5[c]
10.	a-$C_{10}H_7Br$	$C_{10}H_7NHCH_2CH_2CH_2NH_2$	4	89

[a] Reactions have been carried out in refluxing dioxane under an argon atmosphere by using the following concentrations of reactants: 3 mmol of polyamine, 1 mmol of aryl halide, 2 mmol of t-BuONa, 0.5 mol % of $PdCl_2(dppf)$, 1 mol % of dppf. [b] Reported yields correspond to isolated compounds based on aryl halides. [c] In the presence of 5 mol % $PdCl_2(dppf)$and 10 mol % of dppf the yield of products was 41% (entry 8) and 19% (entry 9).

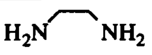
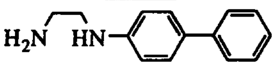
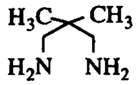
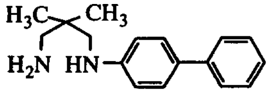
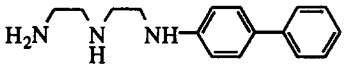
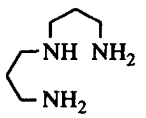
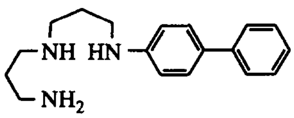
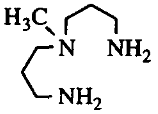
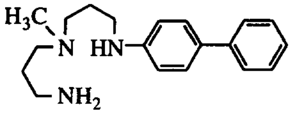
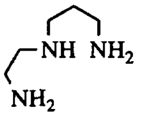
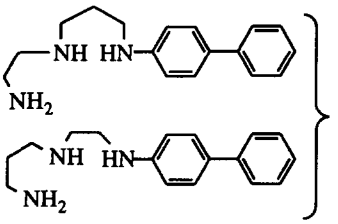
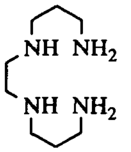
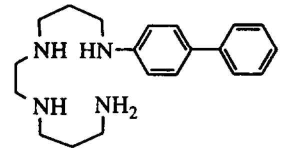
As shown in Table 1, the reaction of 1,3-diaminopropane with aryl halides, bearing a variety of electron-withdrawing and electron-donating substituents in para position, as well as those possessing ortho substituents, provides a general route to arylated 1,3-diaminopropanes. Surprisingly, for all compounds the reaction is highly selective since the reaction products are mainly or only[11] the monoarylated 1,3-diaminopropane derivatives. A clear substituent effect is observed for the arylation of 1,3-diaminopropane. In the case of aryl halides having an electron-withdrawing *p*-(*p*-chlorophenyl)carbonyl (entry 4) or *p*-phenyl (entry 3) substituent we observed an increase in rate of arylation and yields compared to the unsubstituted phenyl compounds (entries 1 and 2). The aryl bromides having electron-withdrawing, base-sensitive groups such as acetyl (entry 6) and trifluoromethyl (entry 5) afford corresponding 1,3-diaminopropanes in moderate yields. On the other hand, the rates of reactions of *p*-iodotoluene, *o*- and *p*-bromoanisole, are low and the reactions generally stop before the aryl halides are completely consumed. The aryl halides substituted by a para electron-donating group react more slowly than those possessing an ortho substituent. In the case of the strong electron-donating methoxy group the desired product is obtained in a low yield (entry 9)[12]. 1-Bromonaphthalene rapidly reacts with 1,3-diaminopropane leading to 1,3-diamino-N-naphthylpropane in 89 % yield (entry 10).

The Pd-catalyzed arylation reaction has been successively employed for the preparation of a variety of aryl substituted polyamine compounds (Equation 2). The experimental data related to the reaction of polyamines with 4-bromobiphenyl are provided in Table 2.



(2)

Table 2. Palladium-Catalyzed Reactions of 4-Bromobiphenyl with Polyamine Compounds [a]

Entry	Amine	Product	Time, h	Yield[b], %
1.			4	64
2.			3	75
3.			4	77
4.			4	77
5.			24	83
6.			24	85[c]
7.			18	88

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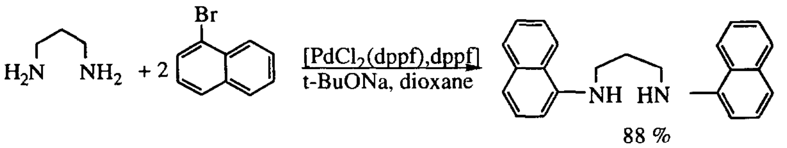
[a] Reactions have been carried out in refluxing dioxane under an argon atmosphere by using the following concentrations of reactants: 3 mmol of polyamine, 1 mmol of 4-bromobiphenyl, 2 mmol of t-BuONa, 1 mol % of $PdCl_2(dppf)$, 2 mol % of dppf. [b] Reported yields correspond to isolated compounds based on 4-bromobiphenyl. [c] A mixture of two regioisomers in the 1:1 ratio is obtained. Isomers are separated using column chromatography on silica gel (CH_2Cl_2; $CH_2Cl_2/CH_3OH/NH_4OH$ - 2/2/1).

The data in Table 2 give examples of monoarylation of different polyamines. The selective monoarylation of primary amino group in the presence of secondary amino groups is clearly observed for all these reactions. In the case of unsymmetrical 1,3-diamino-N-(2-aminoethyl)propane (entry 6) a mixture of two possible regioisomers in the 1:1 molar ratio is obtained. These isomers are separated by column chromatography. A similar reaction is observed for C- or N-substituted polyamine derivatives (entries 2, 5).

Furthermore, we have also studied the synthesis of polyaryl-substituted derivatives of polyamines according to the same procedure in the presence of an excess of 4-bromobenzotrifluorid, 4-bromobiphenyl and 1-bromonaphtalene. Only the most reactive 1-bromonaphthalene gives the disubstituted derivatives. Only primary amino groups react with 1-bromonaphthalene under these conditions and *sym*-dinaphthyl derivatives are obtained in high yields (Equation 3,4).



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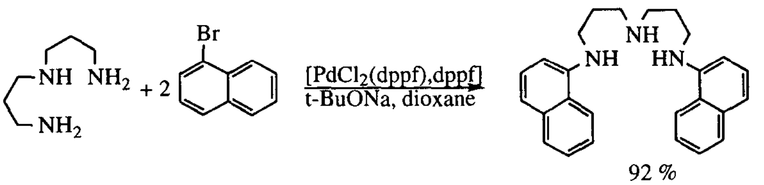

(4)

In conclusion, our preliminary results demonstrate the wide scope of Pd-catalyzed arylation of polyamine compounds. This reaction promises several applications in synthetic organic chemistry such as for the preparation of naturally occurring polyamines and linear or macrocyclic polyaza ligands.

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8. The aryl halides react efficiently only in the presence of sodium *tert*-butoxide as a base.Arylation of 1,3-diaminopropane with 4-bromobiphenyl is not observed without base or in the presence of K_2CO_3. A slow reaction proceeds in the presence of NaOH.
9. Sometimes the excess of dppf increased the rate of arylation (entry 3, Table 1; entry 1,Table 2; but not in the case of entry 4, Table 2).
10. The reaction is carried out until completion (by monitoring GLC analysis of samples) or stopped after 100 h of refluxing. Water is added and the reaction mixture is evaporated in *vacuo*. The residue is taken up in CH_2Cl_2 and the product is extracted from the organic layer with aqueous HCl. After an addition of aqueous solution of NaOH (pH = 12) the product is extracted with CH_2Cl_2. The combined organic layers are dried over Na_2SO_4 and evaporated. An additional purification is performed by column chromatography on SiO_2 (CH_2Cl_2, CH_2Cl_2/CH_3OH /NH_4OH 2/2/1). All compounds are analyzed by IR, ^1H and ^{13}C NMR spectroscopies, and MS spectrometry.
11. Diaryl-substituted products (less than 15%) are observed only in entries 1,2 and 10, Table 1.
12. In the course of submitting of our manuscript the arylation of 2,6-dimethylpiperazine by *p*-$CH_3OC_6H_4Br$ in the presence of $PdCl_2[P(o\text{-}tol)_3]_2$ with rather good yield was published, Zhao, S.-H.; Miller; A.K., Berger, J.; Flippin, L.A. *Tetrahedron Lett.* **1996**, *37*, 4463-4466.

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