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Palladium-catalyzed amination of aryl dibromides with secondary amines: synthetic and mechanistic aspects

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Abstract

Diaminobenzenes are obtained starting from *m*- and *p*-dibromobenzenes and secondary amines in the presence of $Pd(dba)_2/P(o\text{-tolyl})_3$ and sodium *tert*-butoxide in moderate to good yields. Reductive dehalogenation of aryl dibromides is a major side reaction under these conditions. The study of this reaction has shown that the formation of reductive dehalogenation products occurs according to two independent ways. The first one proceeds via the well-known β-hydride elimination from amido-coordinated palladium complexes. The second one involves the formation of hydrido palladium complexes from amino-coordinated derivatives. Although our results do not allow us to propose a detailed mechanistic scheme, they clearly show that the deprotonation step of the catalytic amination cycle has a major effect on the amine/arene ratio.

Keywords: aryl halides; aryl amines; catalysis; palladium.

Aromatic compounds having two or more amino substituents attract considerable attention as components of organic materials and polymers, and simple general methods of their synthesis are still of great interest. Palladium-catalyzed techniques to form aryl amines have recently emerged[1] and prompted intensive studies to synthesize polyamino-substituted benzenes. High yields of double-amination products have been obtained by reacting aryl dibromides with diarylamines or anilines.[2] However, the reaction of dibromobenzenes and primary amines did not afford the desired products due to competing reductive debromination,[3] which also limits the yields in the catalytic amination of aryl halides.[4] In a preliminary communication[5] we have reported a few examples of double amination of *p*-dibromobenzene with secondary amines. Moreover, amination of polybromobenzenes by morpholine has been studied in a parallel work.[6] Here we report results of a detailed study which was performed in order to investigate the double amination of dibromobenzenes with secondary amines and to locate the origin of the reductive dehalogenation which limits the usefulness of catalytic amination of aryl halides, and particularly of aryl dihalides.

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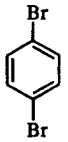
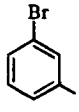
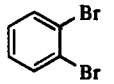
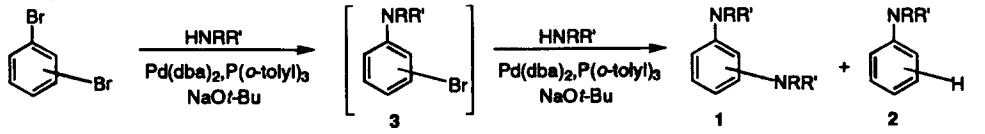
Table 1
Double amination of *m*- and *p*-dibromobenzenes with secondary amines

	Aryl dibromide	Amine	Ligand	Ratio[b] of 1 : 2	Yield[c] of 1,%
1.			$P(o\text{-tolyl})_3$	10:2	76
2.			$P(o\text{-tolyl})_3$[d]	10:1	76
3.			dppf	5:10	–
4.			$P(o\text{-tolyl})_3$	10:6	63
5.			dppf	0:10	–
6.		$HNEt_2$	$P(o\text{-tolyl})_3$	10:5	45
7.			dppf	0:10	–
8.			$P(o\text{-tolyl})_3$	10:1	82
9.			$P(o\text{-tolyl})_3$	10:5	65
10.		$HNEt_2$	$P(o\text{-tolyl})_3$	10:4	58
11.			dppf	0:10	–

[a]Reaction conditions: 1.0 equiv. dihalide, 3.0 equiv. amine, 2.0 equiv. NaO*t*-Bu, 2 mol% $Pd(dba)_2$/ligand, reflux in dioxane under an inert atmosphere. The reaction was carried out until completion (GC monitoring). [b]Relative amount of the reaction products was estimated by GC. Products were also isolated in selected cases to ensure that GC values accurately correspond to products distribution. [c]The yields (based on aryl dihalide) of isolated compounds (column chromatography) are estimated to be more than 95% pure (judged by ^1H and ^{13}C NMR and either GC/MS analysis or combustion analysis). [d]In toluene.

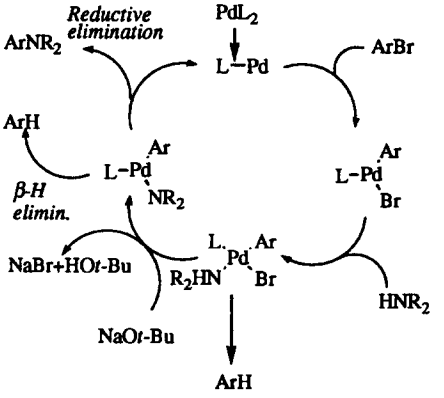
First, secondary cyclic and acyclic amines were reacted with *o*-, *m*- and *p*-dibromobenzenes by using $Pd(dba)_2/P(o\text{-tolyl})_3$[7] as a catalytic precursor and sodium *tert*-butoxide as a base. Under these conditions the amination of *m*- and *p*-dibromobenzenes with an excess of morpholine, piperidine or diethylamine afforded diaminobenzenes **1** in moderate to good yields depending upon the type of amines (Table 1, entries 1, 4, 6, 8–10). A bulky cyclic tetramine like cyclam (1, 4, 8, 11-tetraazacyclotetradecane) did not lead to arylamines under these conditions. The reaction of the sterically hindered *o*-dibromobenzene with the above mentioned amines only gave products of reductive dehalogenation of one of the two bromine atoms.[8]



We have also studied the amination of aryl dibromides in the presence of $Pd(dba)_2$/dppf as a catalytic precursor (Table 1, entries 3, 5, 7, 11).[9] Rather surprisingly,[10] the reaction of *p*- and *o*-dibromobenzenes did not afford the desired products in good yields due to the extensive reductive debromination.

The currently accepted mechanism of aryl halides amination is shown on Scheme 1.[11] All the results obtained to date strongly suggest that both arylamine and arene products result from competitive reductive elimination of amine and β-hydride elimination from an amido aryl intermediate.[12] The mechanism of reductive dehalogenation of aryl bromides does not seem to provide a reasonable explanation of our experimental data. For example, it is difficult to explain why the amount of the reduction product increases when the amine is changed from morpholine (pK_a=8.33) to piperidine (pK_a=11.12) (Table 1, entries 1 and 4).[13] The structure of these amines is rather similar and we would expect a predominant formation of arylamine in the case of piperidine which is more nucleophilic.[14] Our data reveals a second pathway for the reduction and prompted us to investigate the origin of this side reaction which is of great importance for successful catalytic amination. Since the non-catalytic reaction of dibromobenzenes with amines does

not afford any reduction products,[15] this reaction must proceed via palladium-containing intermediates. To elucidate the reaction pathway, it was of major interest to know the rate-determining step of the catalytic cycle. It is clear by considering the reactions involving equimolar amounts of *p*-dibromobenzene and piperidine or diethylamine that bromo aminobenzenes **3**, inevitable intermediate compounds in double-amination reactions, are more reactive with amines than the starting dibromobenzenes since bromoaminobenzenes **3** did not accumulate.[16] The higher reactivity of bromoaminobenzenes **3**, having a strong electron-donating amino substituent on the aryl ring compared to starting dibromobenzenes, may suggest that the oxidative addition of aryl halide to Pd(0) species is not a crucial step under these conditions. On the other hand, the less basic morpholine is more reactive and gives higher yields of diaminobenzenes than piperidine and diethylamine. This is compatible with the assumption that the deprotonation is the rate-determining step of the reaction. Most probably, the reductive dehalogenation involves the formation of hydrido palladium complexes from amino-coordinated palladium derivatives (Scheme 1). In order to verify this assumption, the reaction of *p*-dibromobenzene with morpholine was carried out in the presence of different bases since the nature of the base can only affect the deprotonation step of the catalytic cycle (Table 2). In the presence of weaker bases (KOH or Cs_2CO_3), the reaction proceeds slowly and leads to an increased amount of the reductive product. When $NaN(SiMe_3)_2$, a strongly basic but bulkier reagent, is employed a significant amount of *m*-diaminobenzene is obtained. This result reveals that the direct nucleophilic substitution (aryne mechanism) competes with palladium-catalyzed amination. After subtraction of the amount of diaminobenzene **1** which is formed through this substitution reaction, the ratio of the diaminobenzene **1** to side product monoaminobenzene **2**, produced by catalytic reaction, is lower compared to the case of NaO*t*-Bu. Thus, the use of less basic or/and bulkier bases induces a decrease of the deprotonation rate of coordinated amines and leads to an increased amount of the reduction product arising from the competing reaction.[17] These results are in accordance with the assumption of side reductive dehalogenation reaction involving an amino-coordinated palladium complex.



Scheme 1.

As a conclusion, this study demonstrates the existence of two different pathways which may lead to reductive dehalogenation of aryl dibromides in the course of the catalytic amination. The first one is the well-known β-hydride elimination when amido-coordinated palladium complexes are formed. The second way occurs through amino-coordinated complexes. This latter mechanism is predominant when strongly basic and bulkier amines are used because the deprotonation of coordinated amines is delayed. We have also shown that the double amination reaction of *m*- and *p*-dibromobenzenes with secondary amines in the presence of Pd/P(*o*-tolyl)$_3$ and NaO*t*-Bu is quite general. While the yields of products are moderate to good, the availability of reagents and catalyst, and the simplicity of the procedure suggest that

Table 2
Influence of the base on the reaction of *p*-dibromobenzene with piperidine

Entry	Base	Products and their GC yields	Ratio of 1 : 2
1.	NaO*t*-Bu	**1**(62%), **2**(38%)	10:6
2.	KOH	**1**(53%), **2**(47%)	10:9
3.	Cs_2CO_3	**3**(16%), **1**(7%), **2**(45%), bromobenzene(32%)	10:64
4.	$NaN(SiMe_3)_2$	*p*-**1**(38%), *m*-**1**(12%), **2**(50%)	10:21

the reaction would be useful for a one-pot synthesis of different diaminobenzenes which are frequently observed fragments in a wide variety of syntheses of organic materials including polyazamacrocyclic ligands.

Acknowledgements

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4. The factors which control the product selectivity are not clear and predictable as yet. See: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703 and references cited therein.
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7. dppf=1,1′-Bis(diphenylphosphino)ferrocene, P(*o*-tolyl)$_3$=tri-*o*-tolylphosphine, dba=dibenzylideneacetone.
8. The reaction of *o*-dibromobenzene with morpholine proceeds slowly and gives after reflux (24 h) 13% of *N*-phenylmorpholine, 18% of bromobenzene along with starting dibromide. Piperidine readily reacts with *o*-dibromobenzene affording *N*-phenylpiperidine **2** in 93% yield. The reaction of diethylamine and *o*-dibromobenzene gives 75% of *N,N*-diethylaniline along with 15% of *N*-ethylindole. *N*-ethylindole could be formed by the following route: (1) dehydrogenation of diethylamine followed by its isomerization to the enamine derivative, (2) Heck reaction of *o*-dibromobenzene with this enamine, (3) intramolecular palladium-catalyzed amination affording *N*-ethylindole.
9. It is well-known that chelating ligands provide an enhanced selectivity for the amination over reductive dehalogenation in the catalytic reactions of aryl halides with amines as well as some of aryl polybromides with morpholine. See, e.g.: Refs. 1, 6 and Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993–6996.
10. The same result was obtained in the reaction of 4-*tert*-butylbromobenzene with *N,N*-di-*n*-butylamine. See: Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569.

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13. Moreover, according to the above mechanism one may expect on the basis of the generally accepted ideas that the relative amount of the reduction products would be increased by the use of inert solvents (see, for example: Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163–1188). However, the reaction of *p*-dibromobenzene with morpholine gives a lower yield of reduction product when the reaction is carried out in toluene instead of dioxane (Table 1, entries 1 and 2).
14. Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626–3633.
15. Non-catalytic reduction can play a significant role in the reaction of aryl polybromides with amines. For example, reflux of hexabromobenzene and morpholine in the presence of NaO*t*-Bu for 3 days affords a mixture of reduction and substitution products (^{1}H and ^{13}C NMR data). However, reactions of *p*- and *m*-dibromobenzenes with piperidine in the presence of NaO*t*-Bu proceed very slowly (less than 40% of conversion after 3 days of refluxing) leading to mixtures of products of nucleophilic substitution (aryne mechanism).
16. Even using a 3:1 ratio of *p*-dibromobenzenes to morpholine only results in the formation of *N*-(4-bromophenyl)morpholine **3** (33%) along with diaminobenzene **2** (38%).
17. Our results do not allow us to propose a detailed mechanism of this reaction. However, it should be noted that: (1) the possibility of reduction of aryl halides with amines in the presence of Pd(0) complexes has already been shown (Imai, H.; Nishiguchi, T.; Tanaka, M.; Fukuzumi, K. *J. Org. Chem.* **1977**, *42*, 2309–2313). Although the mechanism of this reaction is not clear, the amido-coordinated palladium complexes do not seem to be involved since pyrrolidine and *N*-methylpyrrolidine have similar reactivity under these conditions; (2) since reduction ceases after the full consumption of the base in the reaction of *p*-dibromobenzene with excess of morpholine and 0.5 equiv. of NaO*t*-Bu (GC/MS analysis), this reduction reaction must be assisted by an external base.