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Solid Phase Synthesis of Aryl Amines

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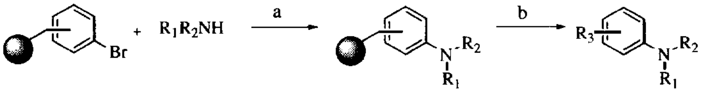
Abstract: *A method for the solid phase synthesis of aryl amines is reported. The method involves a palladium mediated coupling reaction between aryl bromides and amines. The products are isolated in high purity and good yields. This method should prove to be a useful tool for constructing combinatorial libraries containing the aryl amine moiety.* Copyright © 1996 Elsevier Science Ltd

The aryl amine moiety appears repeatedly as a key element in compounds possessing biological activity. As such, a general method for the solid phase synthesis of these molecules would be of tremendous value in developing combinatorial approaches for drug discovery and/or lead optimization. Two important issues for chemisrty used in library synthesis are: (1) chemistry that takes advantage of commercially / readily available starting materials; (2) chemistry that affords products in high purity, minimizing the number of unidentifiable side products in the library. A recent report[1] details the solid phase preparation of some aryl piperazines *via* displacement of an aryl fluoride by a piperazine derivative. A limitation of this method is that the aromatic fragment must contain a nitro group in the *ortho* or *para* position for a clean and complete reaction. The elegant palladium catalyzed cross coupling of aryl bromides and amines recently developed by Buchwald and Hartwig[2] appeared ideal for adaptation to solid phase. Herein we report the successful application of this reaction to the solid phase synthesis of a variety of aryl amine derivatives.

Rapp TentaGel S RAM resin was deprotected and derivatized with several aryl bromides containing either a carboxylic acid or an amine *via* standard coupling reactions[3,4] to afford the polymer bound aryl bromides with either an amide or a urea link. The polymer bound aryl bromides were then allowed to react with amines in the presence of a palladium catalyst (Scheme 1).[5] After screening several phosphines and solvents, reaction conditions were found which afforded the desired aryl amine derivatives in good yield after cleavage from the solid support with 90 % TFA/water. The results are shown in Table 1.

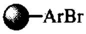
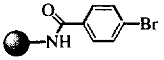
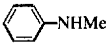
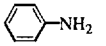
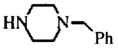
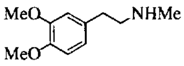
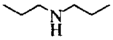
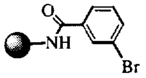
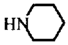
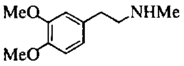
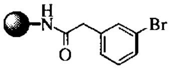
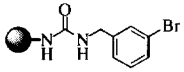
Scheme 1



Reaction Conditions: (a) 0.2 Pd_2dba_3, 0.8 Phosphine, 18 NaO^tBu, Dioxane, 70 -80 °C;
(b) 90 % TFA/water

This method was found to work well for a variety of amines including cyclic and acyclic secondary amines (Table 1, entres 1,4-8) and aniline derivatives (Table 1, entries 2 & 3) when $P(o\text{-tolyl})_3$ was employed as a ligand. In most cases the products were obtained in good to excellent chemical purity as determined by both HPLC[6] and ^1H NMR analysis. The only side product observed arises from substitution of the bromide by a hydrogen (reduction). Since this product is easily identified and is generally only present in minor amounts its presence

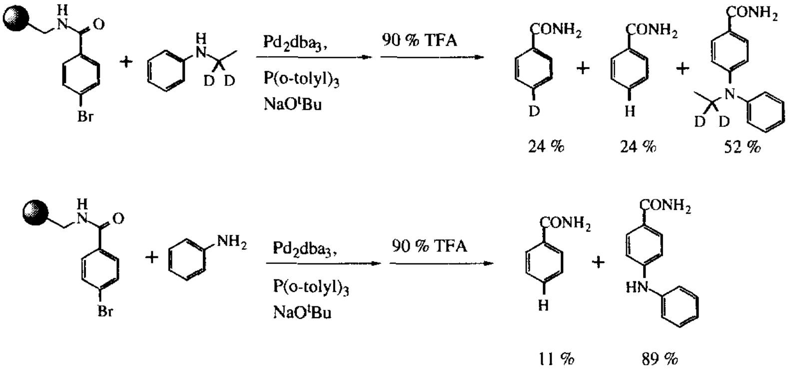
Table 1: Palladium Mediated Coupling of Polymer Bound Aryl Bromides and Amines

Entry		Amine	Yield	Purity	Product Ratio $ArNR_1R_2$ /ArH
1			>95 %	81 %	90 / 10
2	"		>95 %	87 %	89 / 11
3	"		95 %	86 %	89 / 11
4	"		>95 %	82 %	92 / 8
5	"		>95 %	90 %	88 / 12
6	"		>95 %	95 %	96 / 4
7	"		75 %	49 %	66 / 34
8	"		>95 %	80 %	80 / 20
9			>95 %	95 %	96 / 4
10	"		>95 %	88 %	92 / 8
11	"		90 %	86 %	89 / 11
12	"		84 %	85 %	85 / 15
13			>95 %	85 %	92 / 8
14			80 %	50 %	50 / 50

should not be a significant problem in the context of library synthesis. Reaction with primary amines did not provide clean products under these conditions.

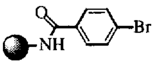
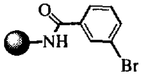
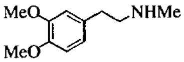
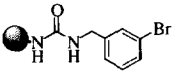
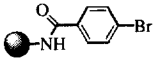
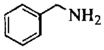
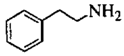
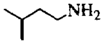
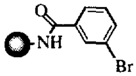
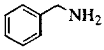
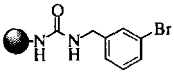
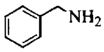
When the aryl bromide was attached to the resin through a urea link up to 50 % of the reduction product was obtained (entry 14). To gain some insight into the mechanism of formation of this product we conducted the experiments shown in Scheme 2. When deuterated ethylaniline was allowed to react under standard conditions the reduction product was found to contain ca. 50 % isotope incorporation. This suggests that one source of the H atom is the carbon α to nitrogen in the amine. A likely mechanism for this is β-hydrogen elimination of the intermediate palladium aryl amido complex followed by reductive elimation.[7] When aniline was coupled under standard conditions 11 % of reduction product was observed, indicating an additional pathway is operative.[8]

Scheme 2



These results prompted us to investigate bisphopshine ligands in the reaction since we expected that an additional ligand bound to palladium would occupy the empty metal orbital required for β-elimation^9 and therefore diminish the amount of reduction product formed. Of the chelating ligands screened, BINAP^{10} was found to give a significant improvement in the product ratios (Table 2). For example, when the 3-bromobenzyl urea resin was allowed to react with morpholine the products were obtained in a 91 / 9 ratio in favor of the desired aryl amine (Table 2, entry 4). This is compared to a 50 / 50 ratio obtained using P(o-tolyl)$_3$ (Table 1, entry 14).

Table 2: Palladium Mediated Coupling of Polymer Bound Aryl Bromides and Amines

Entry	●-ArBr	Amine	Yield	Purity	Product Ratio ArNR$_1$R$_2$ /ArH
1			84 %	93 %	>97 / 3
2			80 %	86 %	92 / 8
3	"		95 %	63 %	83 / 17
4			95 %	65 %	91 / 9
5			87 %	99 %	>97 / 3
6	"		82 %	99 %	>97 / 3
7	"		85 %	95 %	>97 / 3
8			95 %	92 %	97 / 3
9			92 %	89 %	97 / 3

With a less reactive acyclic secondary amine (Table 2, entry 3) no significant change in the product ratio was observed. In fact, in this case, some additional unidentified side products were obtained and the purity of the product was 63 % with BINAP compared to 85 % with P(o-tolyl)$_3$.

Surprisingly, the use of BINAP as a ligand allowed for the successful coupling of primary amines, affording the products in good yields and with excellent purities (Table 2, entries 5-9). Very little of the reduction product is obtained under these conditions, less than 5 % in all cases.

In conclusion we have developed an effective method for the solid phase synthesis of aryl amine derivatives. With the appropriate ligand selection, this chemistry can be successfully used for coupling of primary or secondary amines, affording the products in high chemical purity. This method should prove to be a valuable tool for the construction of combinatorial libraries containing aniline derivatives.

References and Notes:

1. Dankwardt, S. M.; Newman, S. R.; Krstenansky, J. L. *Tetrahedron Lett.* **1995**, *36*, 4923.
2. a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927. b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. c) Luoie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. d) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. e) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348.
3. Aryl bromides were attached through a carboxamide link by coupling of the approriate acid derivative using EDC / DMF.
4. Aryl bromides were attached through a urea link using the method previously reported. Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055.
5. A typical procedure is as follows: In a test tube capped with a rubber septum 150 mg of aryl bromide derivitized resin (1 equiv) and the amine (15 equiv) were suspended in 2 mL of dry dioxane and the vessel was purged with nitrogen for 5 min. A solution of Pd$_2$dba$_3$ (0.2 equiv), P(o-tolyl)$_3$ (0.8 equiv) and sodium *tert*butoxide (18 equiv) in 1 mL dioxane (premixed under nitrogen in a separate flask) was added to the suspension of resin. The mixture was stirred in an oil bath at 70-80 °C for 16-20 h. The resin was then transfered to a fritted vessel and washed with water (2mL), DMF, THF, CH$_2$Cl$_2$, IPA, CH$_2$Cl$_2$ and AcOH (4x2mL each). The products were cleaved by treatment of the resin with 90 % TFA/water for 20 min (2 x). The sample was concentrated and lyophilized from acetic acid.
6. Analysis by HPLC using a 4x100 mm Zorbax SB-C8 column (5μ particle size) with a gradient of 10% acetonitrile/water containing 0.1 % TFA to 100 % acetonitrile over 10 min. Peak areas were integrated at 220 nm.
7. While this work was in progress a similar observation was reported for the solution phase coupling reaction; Hartwig, J. F.; Richards, S,; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.
8. When the reaction was run in d8-dioxane no isotope incorporation was observed in the reduction product. Similarly when the resin was pretreated with 10 % D$_2$O in dioxane followed by coupling under standard conditions no isotope incorporation was observed. These results indicate that reduction through participation of solvent or adventitious moisture is not occuring.
9. R. H. Crabtree, "The Organometallic Chemistry of the Transition Metals" John Wiley and Sons, New York, pp. 154-159.
10. Similar results have been observed in the solution phase reaction; Buchwald, S. L. personal communication. Other chelating ligands such as bisdiphenylphosphinopropane or bisdiphenylphosphinoethane were ineffective in the present work.

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