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Solid Phase Synthesis of Aryl Amines Via Palladium Catalyzed Amination of Resin-Bound Aromatic Bromides

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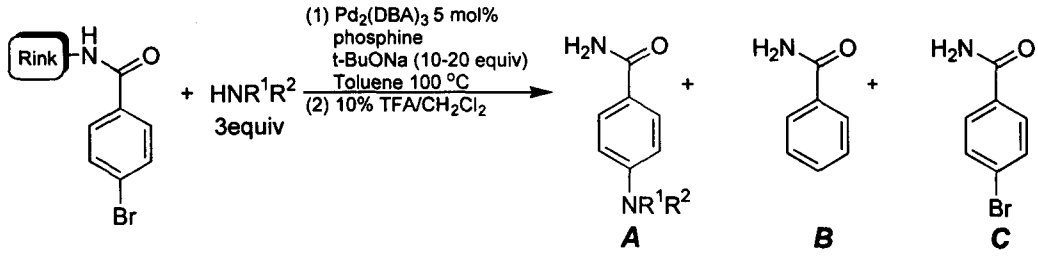
Abstract: Polymer-bound aromatic bromides were found to readily undergo Pd-catalyzed amination with a number of primary and secondary alkyl- and arylamines to give, after cleavage from the support, a variety of arylamine products.

The generation of molecular diversity through combinatorial synthesis promises, in concert with high-throughput biological screening, to deliver a plethora of new drug candidates. A number of methods have been developed for the production of chemical libraries in solid-phase manifolds. The synthesis of small organic molecules on polymer supports requires the redevelopment of solution phase chemistry and a number of such protocols have been recently published.[1] In this communication we disclose a method for the solid phase synthesis of aryl amines from aryl bromides and amines under the palladium (0) catalysis conditions recently developed independently by Buchwald and Hartwig.[2a-b]

The scope of the method was determined by studying the coupling of a model bromide linked to Rink resin[3] (*p*-bromobenzamidyl) with a variety of amines, and by studying the coupling of a variety of resin-bound bromides[4] with two model amines (*ortho*- and *para*-anisidine). The coupling products were cleaved from the resin and characterized by the usual spectroscopic techniques (^{1}H NMR, MS).[5]

With the P(*o*-Tol)$_3$/Pd system both simple aromatic and aliphatic amines could be coupled. However, primary and secondary aliphatic amines gave significant reduction of the bromide (***Table 1***, **Entries 1** and **2**). Utilization of Buchwald's improved method[6] with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) decreased this side reaction to an undetectable level by ^{1}H NMR (***Table 1***, **Entries 3** and **4**). Use of BINAP produced a more reactive catalyst allowing the coupling of more functionalized amines that were nearly completely inactive in couplings using P(*o*-Tol)$_3$ (***Table 1***, compare **Entries 10**, **12**, and **17** with **Entries 11**, **13**, and **18** or **19**), though, in several cases, the conversion of starting material to product was incomplete at 20 hours (***Table 1***, **Entries 9**, **11**, **13**, **16**, and **18**). However, further conversion to product may be effected by an extended reaction period (***Table 1***, compare **Entries 18** and **21** with **Entries 20** and **22**). In addition, we have found that substituting bis(diphenylphosphino)ferrocene (dppf) for BINAP results in a catalyst system that is similar in selectivity and activity (***Table 1***, compare **Entries 4**, **13**, and **18** with **Entries 5**, **14**, and **19**).[7] A number of amines were found to be unreactive under all conditions tried and are listed in endnote 8.[8]

Table 1

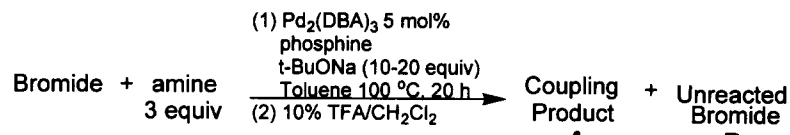


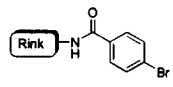
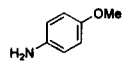
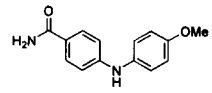
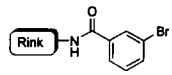
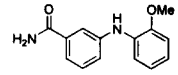
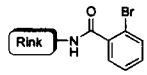
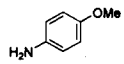
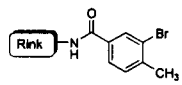
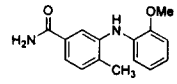
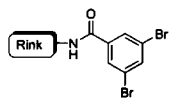
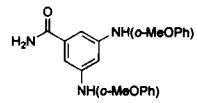
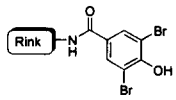
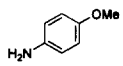
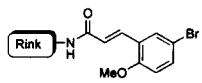
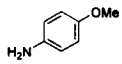
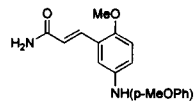
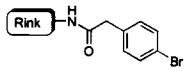
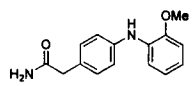
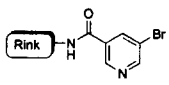
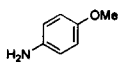
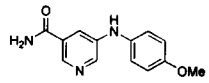
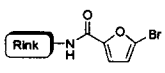
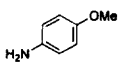
Entry	R^1	R^2	*Phosphine*	*Time*	*A:B:C*
1	$-CH_2CH_2NHCH_2CH_2-$		P(*o*-Tolyl)$_3$	20 h	90:10:0
2	H	(1-phenyl)eth-1-yl	P(*o*-Tolyl)$_3$	20 h	65:35:0
3	$-CH_2CH_2NHCH_2CH_2-$		BINAP	20h	100:0:0
4	H	(1-phenyl)eth-1-yl	BINAP	20 h	100:0:0
5	H	(1-phenyl)eth-1-yl	dppf	20 h	100:0:0
6	H	2,6-dimethylphenyl	P(*o*-Tolyl)$_3$	20 h	100:0:0
7	H	*o*-methoxyphenyl	P(*o*-Tolyl)$_3$	20 h	100:0:0
8	H	*o*-hydroxyphenyl	P(*o*-Tolyl)$_3$	20 h	15:0:85
9	H	*o*-hydroxyphenyl	BINAP	20 h	40:0:60
10	H	*o*-aminophenyl	P(*o*-Tolyl)$_3$	20 h	0:0:100
11	H	*o*-aminophenyl	BINAP	20 h	40:0:60
12	H	*o*-carboxyphenyl	P(*o*-Tolyl)$_3$	20 h	0:0:100
13	H	*o*-carboxyphenyl	BINAP	20 h	60:0:40
14	H	*o*-carboxyphenyl	dppf	20 h	50:0:50
15	H	(2-phenyl)-(1-carboxy)eth-1-yl	BINAP	20 h	95:0:5
16	H	2-pyridyl	BINAP	20 h	85:0:15
17	H	4-pyridyl	P(*o*-Tolyl)$_3$	20 h	0:0:100
18	H	4-pyridyl	BINAP	20 h	40:0:60
19	H	4-pyridyl	dppf	20 h	65:0:35
20	H	4-pyridyl	BINAP	70 h	95:0:5
21	H	2-pyrimidyl	BINAP	20 h	30:0:70
22	H	2-pyrimidyl	BINAP	70 h	100:0:0

A number aromatic bromides were coupled to PS-Rink resin and their couplings were studied with either *ortho*- or *para*-anisidine. All of the bromides studied couple cleanly except for those derived from 2-bromobenzoic acid, 3,5-dibromo-4-hydroxybenzoic acid, and 5-bromofuroic acid which are recovered unreacted after cleavage from the resin (***Table 2***, **Entries 3**, **6**, and **10**). The reason for these failures is not clear.

As before, we found that dppf could substituted for BINAP with no loss in activity (***Table 2***, **Entries 7** and **9**) but, also no improvement in unsuccessful couplings (***Table 2***, **Entries 3**, **6**, and **10**).[9]

Table 2



Entry	*Bromide*	*Amine*	*Phosphine*	*Coupling Product*[a]	*A:B*
1			$P(o\text{-Tol})_3$		100:0
2			$P(o\text{-Tol})_3$		100:0
3			$P(o\text{-Tol})_3$, BINAP, or dppf	No reaction	0:100
4			$P(o\text{-Tol})_3$		100:0
5			$P(o\text{-Tol})_3$		100:0
6			BINAP or dppf	No reaction	0:100
7			dppf		100:0
8			$P(o\text{-Tol})_3$		60:40
9			dppf		100:0
10			$P(o\text{-Tol})_3$, BINAP, or dppf	No reaction	0:100

In conclusion, we have described an approach for the synthesis of a variety of aromatic amines on solid support. The application of this chemistry to the production of a variety of combinatorial libraries for biological screening will be described in due course.

References and notes.

1. (a) Ellman J. A.; Thompson, L. A. *Chem. Rev.* **1996**, *96*, 555-560; (b) Fruchtel, J. S.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1742 and references contained therein.
2. (a) Buchwald, S. L.; Guram, A. S.; Rennels, R. A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348-1350; (b) Hartwig, J. F; Louie, J. *Tetrahedron Lett.*, **1995**, *36*, 3609.
3. Polystyrene Rink resin (loading of 0.82 mmol per gram) was purchased from Advanced ChemTech.
4. The aromatic bromides used in this study were purchased from Aldrich and used without further purification. The substrates were attached to Rink resin through coupling with N,N-diisopropylcarbodiimide and DMAP. Cleavage of the substrates from the resins and weighing the dry residues confirmed the quantitative reaction of the free amino groups.
5. *General Procedures.* The resin (1.0 equiv) was placed in a 25 mL Schlenk tube equipped to a stir bar. A solid mixture of $Pd_2(DBA)_3$ (0.05 equiv), phosphine (0.20 equiv of monophosphine or 0.15 equiv of diphosphine), *t*-BuONa(10-20 equiv; the use of a large excess of base was found to be necessary in order to get reproducible results in cases without *rigorously* dried solvents and reagents), and amine (3.0 equiv) was added to the tube followed by 3.0 mL of dry toluene. The tube was either sealed under vacuum or sealed under oil bubbler pressure of N_2 (equipped with reflux condenser). The tube was placed in an oil bath maintained at 100 °C for 20 or 70 hours. The reaction mixture was filtered on a coarse frit and the resin was washed with 3x5 mL MeOH and 3x5 mL CH_2Cl_2. The coupling product was cleaved by treatment with two cycles of 20% trifluoroacetic acid in CH_2Cl_2 for 5 min each. The combined cleavage solutions were concentrated to dryness and the products were characterized by ^1H NMR and MS. In every case the yields were determined to be essentially quantitative based on the mass of the recovered material.
6. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* in press. We thank Prof. Buchwald for sharing his results prior to publication.
7. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* in press.
8. The following amines could not be coupled under any of the conditions tried: *Ortho-* and *para-*nitroaniline, aminotriazine, 5-aminouracil, 2,6-diaminoanthraquinone, histidine, 2-aminobenzimidazole, imidazole, and pyrazole.
9. **Entries 7** and **9** of ***Table 2*** were performed solely with the dppf/Pd system, however, though not tried, there is no reason to believe that either P(*o*-Tol)$_3$/Pd or BINAP/Pd would not have been successful in these cases.

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