ORGANIC LETTERS

2002
Vol. 4, No. 26
4689−4692

Palladium-Catalyzed Amination of Aryl Halides on Solid Support

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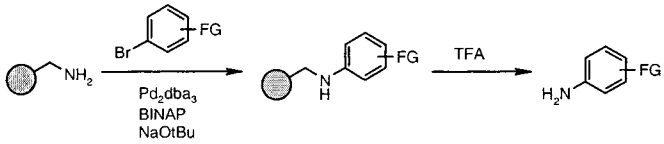
Received October 17, 2002

ABSTRACT

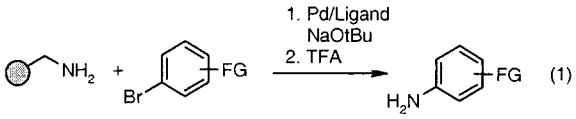


The first examples of the Pd(0)-catalyzed amination of aryl halides using Rink-resins as nitrogen source are described. Pd_2dba_3/BINAP/NaO-*t*-Bu was found to be the most efficient catalyst/base system, while a solvent mixture of dioxane and *tert*-butyl alcohol was shown to enhance the selectivity toward the desired monoarylation. Moderate to good yields and excellent purities of the amination products were found with electron-poor aryl halides, while electon-rich aryl halides failed to react under these conditions.

The arylamine moiety is an ubiquitous structural element in pharmacologically active compounds. The palladium-catalyzed amination of aryl halides, which was developed by the groups of Buchwald[1] and Hartwig,[2] opens an attractive new synthetic route toward this important functional group. While the classical method for the formation of substituted arylamines involves a nitration−reduction and substitution sequence that is often not compatible with other functional groups, the Buchwald−Hartwig amination procedure is broadly applicable to a great variety of substrates and nitrogen donors and uses milder conditions. In 1996, Ward[3] and Willoughby[4] reported independently their first successful application of the Buchwald−Hartwig amination procedure on solid support. Both groups immobilized the aryl bromides via an amide linkage onto the resin and added a large excess of the amine. The undesired reduction of the aryl bromides via β-hydride elimination could be minimized through the use of chelating phosphine ligands such as BINAP or dppf. The Pd-catalyzed amination of 2-chloropurines immobilized on a solid support was described recently.[5]

In the course of developing synthetic routes toward an arylamine library on solid support, we became interested in investigating the use of amine resins as nitrogen sources in palladium-catalyzed C−N cross-couplings (Scheme 1). In this paper, we report our initial results for the coupling of functionalized aryl halides to acid-labile amine-based solid supports as nitrogen donors.

Scheme 1



In an initial study, we tested seven resins for their ability to undergo the desired reaction. Thus, amino-functionalized polystyrene resins with Rink,[6] Knorr, Sieber,[7] DCHD,[8] and 2-chlorotritylamine linkers as well as TentaGel resins with

(1) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

(2) (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.

(3) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993−6996.

(4) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181−7184.

(5) Brill, W. K.-D.; Riva-Toniolo, C.; Müller, S. *Synlett* **2001**, 1097−1100.

(6) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787−3790. Rink amide resin was purchased from Advanced ChemTech.

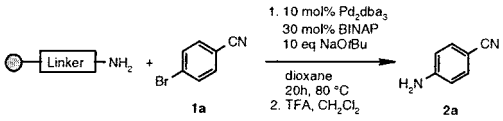
(7) Sieber, P. *Tetrahedron Lett.* **1987**, *28*, 2107−2110. Sieber amide resin was purchased from Bachem.

(8) Ramage, R.; Irving, S. L.; McInnes, C. *Tetrahedron Lett.* **1993**, *34*, 6599−6602. DCHD resin was purchased from Advanced ChemTech.

10.1021/ol027119s CCC: $22.00
Published on Web 11/27/2002

a PAL[9] and a Rink linker (TentaGel S AM and TentaGel S RAM, respectively)[10] were reacted with excess 4-bromobenzonitrile (**1a**) under the conditions given in Table 1.

Table 1. Coupling of 4-Bromobenzonitrile to Amine Resins[a]



1a 2a

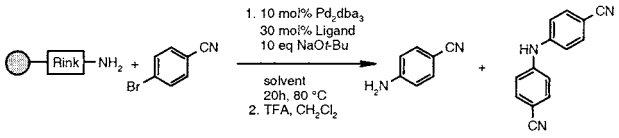
	4-aminobenzonitrile	
linker	yield[b] (%)	purity[c] (%)
Rink	63[d]	87
Knorr	64	92
Sieber	28	53
DCHD	36	86
Tentagel S AM	49	90
Tentagel S RAM	31	92
2-chlorotritylamine	traces[e]	

[a] Reaction performed on 0.03−0.07 mmol scale with respect to the amino groups. [b] Quantitated by calibrated HPLC. [c] Determined by HPLC of the crude product. [d] No product was formed in the absence of Pd. [e] Reaction performed with 10 mol % Pd on a 0.3 mmol scale.

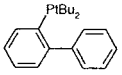
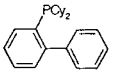
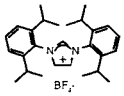
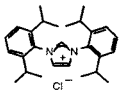
After 20 h reaction time in dioxane, all resins gave a negative Kaiser test, indicating complete consumption of free amino groups. The resin was thoroughly washed, dried, and submitted to TFA cleavage. Gratifyingly, polystyrene resins fitted with the Rink or the Knorr linker gave the expected 4-aminobenzonitrile (**2a**) in good yield and purity. The less hindered Sieber xanthydrylamine polystyrene and DCHD solid supports gave only a minor yield of **2a**. From the two Tentagel resins tested, only the SAM resin fitted with the PAL-linker gave a medium yield. In contrast to the polystyrene-based Rink-amide, the Tentagel S RAM resin with the Rink-amide linker gave an unsatisfactory yield of **2a**. No product could be isolated from the 2-chlorotritylamine resin. In some cases, minor amounts (up to 5 mol % with respect to the active sites of the resins) of benzonitrile, formed by β-hydride elimination, could be detected in the washing solutions. A second cycle of TFA-treatment did not yield any additional product. We therefore assume that degradation of the resin under the reaction conditions accounts for the incomplete mass balance.[11] To confirm that the reaction does not proceed via an S_NAr mechanism we also submitted the Rink amide resin to the reaction without adding a palladium source. We could not detect any aniline product under these conditions.

We next investigated the most suitable combination of ligand and solvent. Table 2 summarizes the conversion of our standard substrate **1a** with the polystyrene Rink amine resin using different types of ligands.

Table 2. Evaluation of Ligand and Solvent for Coupling of 4-Bromobenzonitrile (**1a**) to Rink Resin[a]



1a 2a 3a

entry	ligand	solvent	**2a** [%][b,c]	**3a** [%]
1	BINAP	dioxane	63 (87)	4
2	BINAP	dioxane/ *t*-BuOH 1:1	80 (94)[d]	0
3	dppf[e]	dioxane/ *t*-BuOH 1:1	58 (94)	0
4		dioxane/ *t*-BuOH 1:1	44 (94)	0
5		dioxane	39 (87)	2
6	P(*t*-Bu)$_3$	dioxane/ *t*-BuOH 1:1	8 (75)	0
7		dioxane	63 (89)	6
8		dioxane	58 (87)	9

[a] Reaction performed on 0.03−0.07 mmol scale with respect to the amino groups on the resin. [b] Quantitated by calibrated HPLC. [c] In parentheses: purity determined by HPLC of the crude product. [d] 83% isolated yield. [e] 20 mol % $Pd(OAc)_2$ used instead of Pd_2dba_3.

NaO-*t*-Bu was again used as the base. A large excess of both bromide and base (10 equiv of each with respect to the amino groups of the resin) were used to ensure complete reaction. Both BINAP[12] and dppf efficiently catalyzed the desired coupling of **1a** to the resin, with BINAP leading to somewhat higher yields.

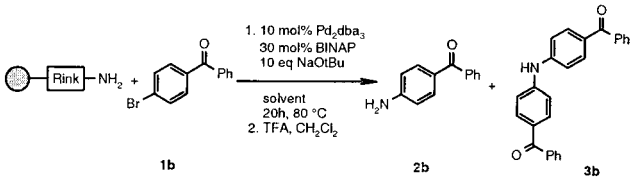
In addition, a series of monodentate alkylphosphine ligands[13,14] were tested (entries 4−6) but found to be inferior to BINAP. The two carbene ligands[15] we tested (entries 7 and 8) were found to be as effective as the BINAP ligand.

Not unexpectedly, the high amount of aryl bromide in the reaction mixture led to the formation of minor quantities of the doubly arylated product bis(4-cyanophenyl)amine (**3a**)

(9) Albericio, F.; Kneib-Cordonier, N.; Biancalana, S.; L.; Masada, R. I.; Huson, D.; Barany, G.*J. Org. Chem.* **1990**, *55*, 3730−3743.
(10) TentaGel resins were purchased from Advanced ChemTech.
(11) Gauzy, L.; Le Merrer, Y.; Depezay, J.-C.; Clerc, F.; Mignani, S. *Tetrahedron Lett.* **1999**, *40*, 6005−6008.
(12) For a review on the Pd/BINAP-system in the amination of aryl bromides see: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157.
(13) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.
(14) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem.* **1999**, *111*, 2570−2573. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

in some cases, especially with BINAP and the carbene ligands (Table 2, entries 1, 7, and 8). When phosphines were used as ligands, this side reaction could be minimized by utilizing a 1:1 mixture of dioxane and *tert*-butyl alcohol as the solvent. The beneficial effect of *tert*-butyl alcohol as cosolvent was found to be even more pronounced with 4-bromobenzophenone (**1b**) as the electrophile (Table 3).

Table 3. Effect of Cosolvent and Stoichiometry on the Ratio of Mono- and Diarylation of 4-Bromobenzophenone (**1b**)



entry	% DVB	equiv of **1b**	solvent	**2b**/**3b**[a]	yield **2b**[b] (%)
1	1	2	dioxane	57:43	50
2	1	10	dioxane/*t*-BuOH (1:1)	80:20	71
3	1	2	dioxane/*t*-BuOH (1:1)	100:0	73
4	2	10	dioxane	94:6	60
5	2	10	dioxane/*t*-BuOH (1:1)	100:0	76

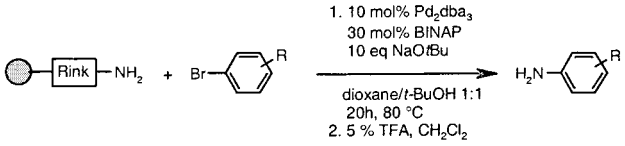
[a] Determined by HPLC analysis of the crude product. [b] Quantitated by calibrated HPLC.

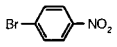
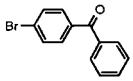
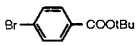
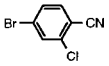
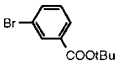
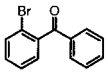
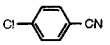
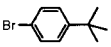
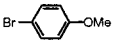
This bromide showed a high tendency toward double arylation of Rink amine resin. Using only 2 equiv of **1b** with respect to the amino groups on the resin in pure dioxane as solvent resulted in a 57:43 mixture of **2b** and the diarylation product **3b**. In contrast, in a 1:1 dioxane/*tert*-butyl alcohol solvent mixture, even with a 10-fold excess of **1b**, an improved ratio of 4:1 in favor of **2b** was found. The formation of **3b** could be completely inhibited by applying only 2 equiv of **1b** in a 1:1 dioxane/*tert*-butyl alcohol mixture. With carbene ligands, no product could be isolated when *tert*-butanol was applied as cosolvent, probably due to the competitive formation of a complex with the alcohol.[16]

We speculated that the reduced swelling of the resin in the more polar solvent mixture might lead to a less accessible environment in which a second arylation is more difficult due to steric reasons. This was supported by a control experiment in which the rink amine was attached to a support with reduced swelling capacity (polystyrene cross-linked with 2% divinylbenzene). Using this resin indeed gave an improved ratio of mono- and diarylation (Table 3, entries 4 and 5). Other solvents such as THF, toluene, or DME served similarly well when used as a 1:1 mixture with *tert*-butyl alcohol while NMP and DMF in general gave poor results (data not shown).

Having established a suitable combination of solvent, resin, additive and catalyst, we explored the scope of the new protocol. A diverse series of aryl bromides bearing functional groups for further elaboration were attached to the resin using the conditions given in Table 4.[17] Aryl bromides with

Table 4. Palladium-Catalyzed Coupling of Aryl Halides with Diverse Functional Groups to Polystyrene Rink Amine Resin



entry	aryl halide	yield [%][a]	purity [%][b]
1		57[c]	95
2		73[d]	96
3		46[e]	96
4		63[f]	95
5		52	94
6		44	96
7		13	76
8		48	90
9		22	91
10		78	95
11		4	32
12		-	-

[a] Quantitated by calibrated HPLC. [b] Purity determined by HPLC of the crude product. [c] 83% yield and 91% purity with THF as solvent and $Pd(OAc)_2$ instead of Pd_2dba_3. [d] 2 equiv of 4-bromobenzophenone were used. [e] In addition, 21% *p*-aminobenzoic acid was formed. [f] Toluene was used as solvent.

electron-withdrawing groups in meta or para-position could be coupled efficiently under Buchwald−Hartwig conditions to give, after TFA-cleavage, the expected anilines in moderate to good yield and excellent purity. The comparatively low yield in the coupling of 3- and 4-bromobenzoic acid

(15) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523−14534. Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119−122. Zhang, C.; Huang, J.; Trudell, M. T.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *Org. Lett.* **1999**, *1*, 1307−1309. Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309. Grasa, G. A.; Mihai S. V.; Huang, J. Nolan, S. P. J. *Org. Chem.* **2001**, *66*, 7729−7737. Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426.

(16) Hocker, J.; Merten, R. *Chem. Ber.* **1972**, *105*, 1651−1663.

tert-butyl ester is due to the concomitant cleavage of the *tert*-butyl ester during TFA-treatment. Ortho-substituted aryl bromides could also be coupled (entries 8 and 9), albeit giving significantly reduced yields compared to their meta- and para-isomers. Unexpectedly, even the electron-poor 4-*chloro*benzonitrile could be coupled efficiently to the Rink amine resin under Pd−BINAP catalysis (entry 10).

Electron-rich aryl halides (entries 11 and 12) gave complex product mixtures containing only minor amounts of the desired amination products, while a negative Kaiser test indicated the absence of amino groups on the resin after the reaction was stopped. Although BINAP is known to be effective for the amination of heterocyclic aryl halides,[18] we could not couple nitrogen and sulfur heterocycles (e.g., 2-chloropyridine, 2- and 3-bromothiophene, 5-bromopyrimidine) to the resin under these conditions.

In summary, we have developed a novel strategy to attach electron-poor aromatics to amine resins which should be useful for the design and synthesis of combinatorial libraries containing arylamine moieties. Investigations into the extension of this methodology to electron-rich aromatics using modified linkers are under way.

Acknowledgment. We thank Prof. Johannes Fröhlich, Technical University of Vienna, for support and helpful discussions.

Supporting Information Available: Text giving representative procedures, a detailed description of the HPLC calibration method, HPLC analyses of the crude products from Tables 1 and 3, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027119S

(17) **General Procedure for the Amination of Amine Resins.** The amination of Rink resin is representative: For Fmoc-deprotection, 100 mg of Rink resin (0.6 mmol/g) was suspended in 2 mL of 20% piperidine/DMF at room temperature for 30 min. The resin was washed with DMF, and the deprotection was repeated for additional 30 min. The resin was washed thoroughly with DMF, CH_2Cl_2, MeOH and CH_2Cl_2 and dried in vacuo. In an oven-dried Schlenk tube purged with argon, the deprotected resin was suspended in 1.5 mL of anhydrous dioxane/*tert*-butyl alcohol 1:1. After 5 min of stirring, 109 mg (0.6 mmol, 10 equiv) of 4-bromobenzonitrile was added. After 10 min of stirring, a mixture of 5.6 mg (0.006 mmol, 0.2 equiv based on Pd) of Pd_2dba_3, 11.2 mg (0.018 mmol, 0.3 equiv) of BINAP, and 57.6 mg (0.6 mmol, 10 equiv) of NaO-*t*-Bu were added as solid. The flask was purged with argon for a few minutes, and the mixture was stirred in an oil bath at 80 °C for 18−20 h. The reaction mixture was then transferred to a frit and washed with CH_2Cl_2, MeOH, CH_2Cl_2, DMF, THF, CH_2Cl_2, MeOH, and CH_2Cl_2. The product was cleaved from the solid support by treatment with 5% TFA/CH_2Cl_2 for 45 min. The resin was filtered off and washed twice with 2 mL of CH_2Cl_2, and the combined solutions were evaporated to dryness. The crude product was dissolved in ethyl acetate and washed twice with saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, evaporated, and dried in vacuo. The residue was dissolved in acetonitrile to give a 1 mg/mL solution that was then analyzed by HPLC.

(18) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241.