Pergamon

Tetrahedron Letters 40 (1999) 415–418

TETRAHEDRON LETTERS

Palladium-Catalyzed Coupling of Functionalized Bromoarenes to a Polystyrene-Bound Aryl Tributylstannane

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Received 15 September 1998; accepted 27 October 1998

Abstract. The Stille reaction with a polystyrene-bound stannyl component, catalyzed by a palladacycle complex, provides a convenient and clean method for the synthesis of substituted biaryls on the resin. Several functional groups useful for the construction of supported polydentate amino alcohols were successfully introduced.

The combinatorial synthesis and testing of chiral metal complex catalysts on solid supports is an exciting strategy for synthetic methods development.[1] In certain cases, such as those involving Lewis acidic metal centers, it would be helpful to employ linkage reactions that avoid the creation of unwanted donor groups. For example, "missed" linkage sites (those that fail to undergo a desired connection to a ligand or ligand precursor) ought not to contain residues that can later compete with the intended ligand(s) for metal binding. Our solution to this problem involves the development of uniquely nonpolar linkers (to be described separately) bearing attachment "handles" that are unreactive toward Lewis acids and to most other reagents. Aryl halides and trialkylstannyl residues, which are married conveniently by palladium-catalyzed coupling reactions,[2] fulfill this requirement, since aryl halides are often inert and aryl trialkylstannanes can be converted to unsubstituted arenes by simple protiodestannylation. Here we report the use of the Stille reaction for the cross-coupling of polymer-bound components to solution-phase species, using a simple model linker system. Although many reports of Pd-catalyzed coupling reactions involving "solid-phase" reagents have appeared,[3] we have found several popular catalyst systems either to be unreliable or to leave behind unwanted deposits of insoluble metal byproducts. The results described here are notable for the use of a catalyst not yet widely employed for the Stille process and for the clean nature of the products formed. The construction of polydentate amino alcohol ligands using this methodology is also demonstrated.

Commercially available 1% divinylbenzene-crosslinked Merrifield resin (0.6 mmol CH_2Cl per gram) was derivatized with 4-tri-*n*-butylstannylbenzoic acid[4] to give the resin bound arylstannane **1** (Figure 1). Treatment of resin **1** with catalytic NaOMe in 4:1 THF:MeOH resulted in complete cleavage of the ester as indicated by IR spectroscopy of the resin before and after the reaction. The amount of methyl benzoate ester recovered from this process corresponded to the presence of 0.32 ± 0.2 mmol of tin per gram of resin **1**, a loading that was consistently observed in several batches and in repeated cleavage experiments.[5] Placing the

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02384-3

arylstannane fragment on the resin reduces both the cost of starting materials (since the solution-phase coupling components are used in excess) and the hazards associated with exposure to tin. Our work also confirms a previous report that such Stille couplings proceed more efficiently when the stannane component is placed on the solid support.[6]

Several well-established catalyst systems were tested in the coupling of **1** to 4-bromoanisole. $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ gave inconsistent or unsatisfactory results under a variety of conditions. $Pd(AsPh_3)_4$ in N-methylpyrrolidinone (NMP), an extremely active solution-phase catalyst mixture,[7] gave good coupling yields but also deposited large amounts of palladium black, which is difficult to separate from polystyrene resins. Ultimately, palladacycle **2**, a highly active and stable catalyst for Heck olefination,[8] proved to be an excellent alternative that gave little or no insoluble palladium byproducts.

Yields of solution phase coupling reactions between 4-tri-*n*-butylstannylanisole and a selection of bromoarenes, catalyzed by **2** in NMP at 90°C, are shown in Figure 1.[9,10] The conditions were optimized for 4-bromoanisole, for which the rate was doubled by the addition of three equivalents of LiCl with respect to the aryl bromide. While as little as 0.1 mol-% of **2** was found to be effective, 5 mol-% catalyst was typically used to reduce the reaction time to approximately five hours.

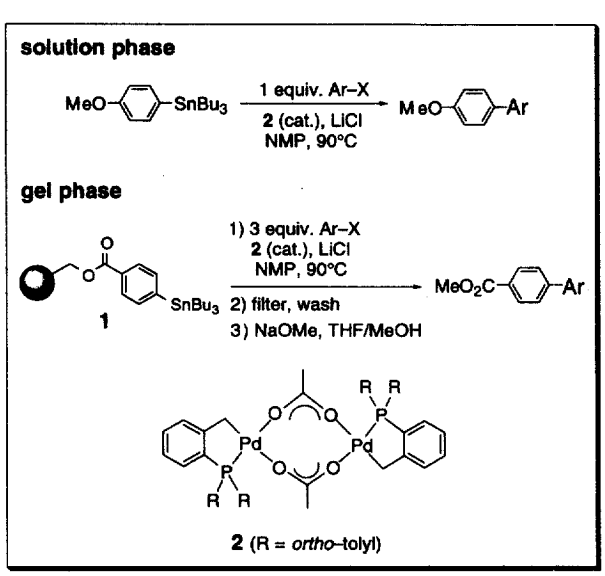
The bromoarenes were chosen to provide an indication of the tolerance of the coupling process to functional groups of interest in the construction of polyfunctional ligands suitable for metal binding. Only the substrate bearing an unprotected 1,2-amino alcohol group did not react under standard conditions, possibly due to chelation of the palladium center. Protection of the amine allowed the coupling to occur in low yields. Reactions with terminal epoxides were performed without added LiCl to eliminate the production of a small amount of chlorohydrin which was otherwise observed.

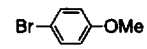
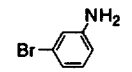
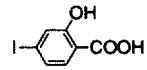
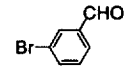
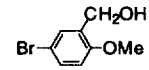
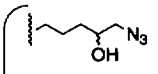
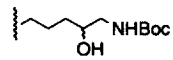
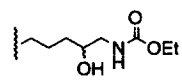
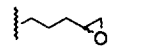
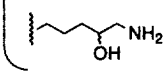
The analogous coupling reactions on the solid support proceeded smoothly. Typically, the resin was added to a solution of the aryl bromide, LiCl, and 5 mol% of **2** in dry degassed NMP. The reaction mixture was made a free-flowing slurry by the addition of additional NMP if necessary, and then was heated to 90°C for 18 h. After cooling to room temperature, the resins were filtered, extensively washed,[12] and dried for several hours under vacuum. Cleavage of the coupling product from the resin was achieved by refluxing in 4:1 THF: MeOH with a catalytic amount of NaOMe.[13] The crude biphenyls isolated by filtration were generally clean, showing a single peak in HPLC or GC analysis, and were obtained in excellent, often quantitative, yield with respect to the starting amount of resin-bound aryl tributylstannane. Analytically pure samples were obtained by flash chromatography. Note that amine, aldehyde, azide, alcohol, carbamate, and epoxide groups are well tolerated.

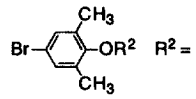
These results show the palladacycle catalyst **2** to be a robust and active system for solid-phase Stille reactions. We are currently applying this and related technologies to the construction of polyfunctional ligands on polymeric supports.

Acknowledgments. Support from the University of Virginia and the National Science Foundation are gratefully acknowledged.

Figure 1. Isolated yield (%) of coupling reactions catalyzed by palladium complex **2**.[11]



Ar–X	% yield solution phase	% yield gel phase
	85	>95
	56	>95
	55	
	75	>95
	70	
	71	>95
	30	80
	30	
	83	>95
	0	0



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4. Prepared by Pd-catalyzed stannylation of ethyl 4-bromobenzoate [$(Bu_3Sn)_2$, $Pd(PPh_3)_4$, refluxing toluene]. followed by saponification (KOH, aq. EtOH).
5. This represents a substitution yield of 67%, accounting for the change in mass of the polymer substituents. No effort was made to force the substitution reactions to completion, although we have done so for alkoxide nucleophiles.
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9. Temperatures in excess of 80°C are needed to activate the catalyst; see Louie, J.; Hartwig, J.F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2359-2361.
10. General procedure for solution-phase coupling reactions: a solution of aryl bromide (0.1–1 mmol), LiCl (3 equiv), and **2** (0.05 equiv) in NMP (1–5 mL) was degassed and treated with 4-(tributyltin)anisole (1.2 equiv) in 1–5 mL NMP. The mixture was sealed in a vial under nitrogen atmosphere and heated at 90°C for approximately 5 h in an oil bath. After cooling to room temperature, the reaction was quenched by adding saturated aqueous KF (1 mL). The resulting mixture was filtered through a pad of celite, and was then diluted with diethyl ether. After washing with 10% HCl, water, and brine, the organic phase was dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by column chromatography (silica gel, petroleum ether/EtOAc) afforded the biphenyl products.
11. 4-Iodosalicylic acid (third entry in the column of Figure 1) produced a biaryl containing an $OSnBu_3$ residue, either on the phenol or carboxylic acid group. This was easily removed prior to final purification by treatment with aqueous acid.
12. DMA (2x), dioxane (2x), saturated KCN in DMSO (1 x 5 min. to remove any Pd black that may be deposited, water (2x), methanol (2x), CH_2Cl_2 (2x).
13. Cleavage of coupling products from the support was typically performed on 100 mg resin samples by treatment of a 4:1 THF:MeOH (10 mL) suspension with 3 drops of 0.5 M methanolic NaOMe, followed by heating to reflux for 12 hours. The resin was filtered and washed with THF (5 mL), MeOH (5 mL), and 1:1 THF: MeOH (5 mL). The collected solution was evaporated and the residue dissolved in 5 mL EtOAc and filtered through a fiberglass filter plug. The solvent was removed and the residue purified if necessary by passage through a plug of silica gel, eluting with a petroleum ether–EtOAc mixture.