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Discovery and synthesis of novel phosphine-based ligands for aryl aminations

Robert A. Singer, Norma J. Tom,* Heather N. Frost and Wendy M. Simon

Pfizer Global Research and Development, Chemical Research and Development, Eastern Point Road, Groton, CT 06340, USA

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Abstract—Three families of ligands were prepared for use in Pd-catalyzed aryl aminations and possibly other Pd-catalyzed reactions. The first series is derived from diarylsulfones, the second from trityl imidazole, and the third from 2-bromobenzophenone. While these ligands were not very general in terms of substrate scope, they do work fairly well under certain specific conditions. Additionally, the preparation of these ligands is amenable to bulk synthesis.

The preparation of arylamines has proven to be an important topic in organic synthesis. Arylamines have been shown to be effective targets for pharmaceuticals and other biologically active molecules.[1] Palladium-catalyzed aminations of aryl halides have been shown to be a mild and effective method of synthesizing arylamines.[2] While there have been remarkable advances in the scope of palladium-catalyzed aminations, we initiated our own program to ensure freedom to operate in this area. It was our goal to design novel ligands that could be easily prepared in bulk quantities that will participate in palladium-catalyzed aminations and possibly other palladium-catalyzed processes.[3] The work described in this paper focuses on three families of ligands that were designed to mimic Buchwald's monodentate biarylphosphine ligands that have been shown to be fairly general in scope for catalyzing aminations of aryl halides.[4] While Buchwald's ligands have been shown to be highly useful for aryl aminations, the synthesis of the ligands can be rather complicated. Our goal was to design ligands that could be easily prepared in large quantities with a minimal number of steps from commercially available starting materials. Towards this end, we targeted three different series; the sulfone ligands **1**, the imidazole ligands **2**, and the '*exo*-olefin' ligand **3**.

As shown in Scheme 1, the sulfone ligands are prepared in one step by *ortho*-metalation with *n*-BuLi of commercially available phenylsulfone or a substituted diarylsulfone, followed by addition of the dialkylchlorophosphine. The product phosphine can be isolated in pure form by recrystallization from isopropanol. The imidazole ligands are prepared from trityl imidazole via metalation with *n*-BuLi, followed by addition of the dialkylchlorophosphine. Again, pure product is isolated by recrystallization from isopropanol. Unfortunately, the synthesis of the *exo*-olefin ligands was slightly more complicated. The Petasis reagent, which was prepared according to literature procedures,[5] was used to install the olefin moiety. Thus, treatment of 2-bromobenzophenone with the Petasis reagent afforded the *exo*-olefin. Metal–halogen exchange was accomplished with *n*-BuLi and the anion was then quenched with the dialkylchlorophosphine. Pure product is obtained by recrystallization from ethanol. While there are probably better ways to synthesize this class of ligands, at this point, it was not efficient to optimize the synthesis of this unproven ligand. We were pleasantly surprised to find that these ligands were remarkably air stable. Samples sitting on the benchtop for several months retained their catalytic activity. These ligands were even stable to silica gel chromatography as early samples were purified via this method.

To demonstrate the efficacy of these new phosphine ligands, four amines were reacted with three aryl halides as shown in Table 1. Standard conditions were 1.0 equiv

Keywords: Pd-catalyzed aryl amination; Phosphine ligands.
* Corresponding author. Tel.: +1-860-715-5270; fax: +1-860-441-5540; e-mail: norma_j_tom@groton.pfizer.com

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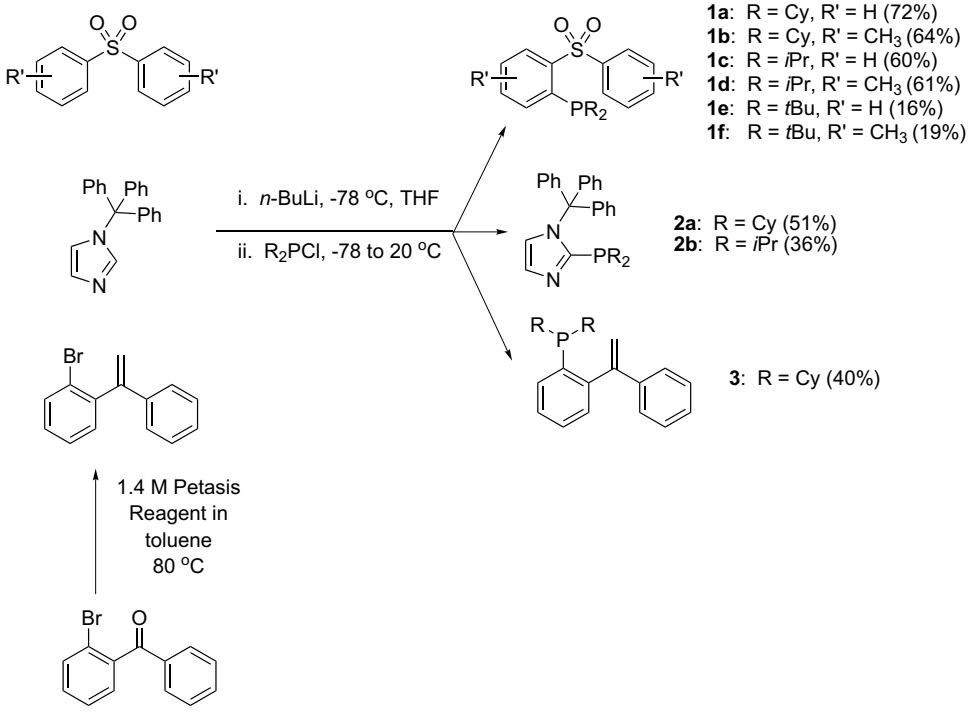


Scheme 1.

Table 1

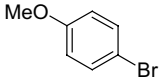
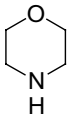
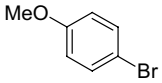
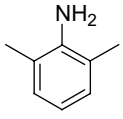
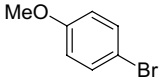
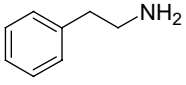
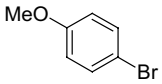
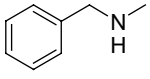
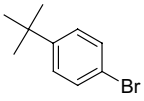
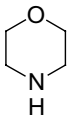
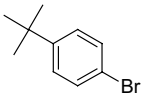
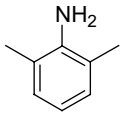
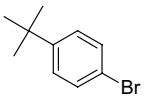
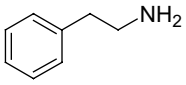
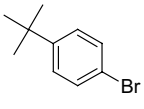
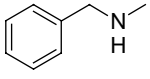
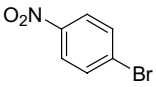
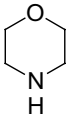
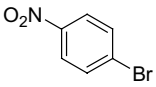
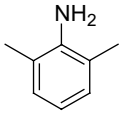
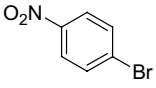
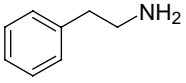
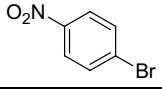
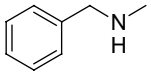
Entry	Aryl halide	Amine	Yield (%) with **1b**	Yield (%) with **2a**	Yield (%) with **3**
1[a]			52	87	96
2[b]			91	82	85
3			N/A	N/A	9
4			12	55	49
5[c]			79	81	60
6[d]			63	59	72
7			N/A	12	N/A
8			38	43	42

Table 1 (*continued*)

Entry	Aryl halide	Amine	Yield (%) with **1b**	Yield (%) with **2a**	Yield (%) with **3**
9[e]			97	78	84
10			87	50–60[f]	58
11			N/A	N/A	N/A
12			87	67	50

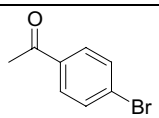
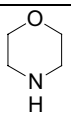
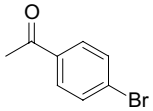
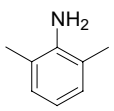
[a] 83%.[4a]
[b] 90% With aniline.[4a]
[c] 86%.[4a]
[d] 87% With aniline.[4a]
[e] 83% With BINAP.[4c]
[f] Yield determined by HPLC as reaction did not proceed to completion.

of the aryl halide, 1.1–1.2 equiv of the amine, 1.3 equiv of sodium *t*-butoxide or cesium carbonate (when the aryl halide contains functionality not compatible with a strong base), 0.05 equiv of palladium acetate, and 0.06 equiv of the ligand in 10 volumes (relative to the halide) of toluene at 100 °C for 2–24 h. For all three series of phosphine ligands, electron-rich 4-bromoanisole and 4-bromo-*t*-butylbenzene were viable substrates with morpholine and 2,6-dimethylaniline. Yields were moderate to excellent. For the primary amine, only trace product was observed, with dehalogenation of the halide being the major side reaction. For the secondary acyclic amine, *N*-methylbenzylamine, moderate yields were obtained. Again, the major by-product was dehalogenation of the aryl halide. With the electron poor substrate, 4-nitrobromobenzene, the sulfone ligands proved to be very effective for morpholine, 2,6-dimethylaniline, and *N*-methylbenzylamine, with yields between 87% to nearly quantitative, while the other ligands afforded the aminated products in moderate to good yields. Unfortunately, none of the ligands formed competent catalysts for primary amines.

These ligands were briefly examined with 4-bromoacetophenone as the halide and morpholine and 2,6-dimethylaniline as the amine (See Table 2). Both ligands **1b** and **3** provided desired product in moderate yields. It was interesting to note that the major by-product with ligand **1b** was ketone arylation of the product. With some optimization, ligand **1b** might be competent in catalyzing ketone arylations.

In summary, we have prepared three families of phosphine ligands for use in the palladium-catalyzed amination reaction. Both ligands **1** and **2** could be readily prepared in one step by metalation with *n*-BuLi, followed by trapping of the anion with a chlorodialkylphosphine. Thus, these ligands are amenable to bulk synthesis. While these ligands were not very general in terms of substrate scope, they do work fairly well under certain specific conditions. These ligands do not have the general scope or the exceptional catalytic activity demonstrated by Buchwald's biaryl ligands, but the ease of preparation justifies their use in certain cases where they have been found to be effective.

Table 2

Entry	Halide	Amine	Yield (%) with **1b**	Yield (%) with **3**
1			58	58
2[a]			33	40

[a] 96% With aniline.[4a]

1. Experimental section

1.1. Dicyclohexyl-[5-methyl-2-(toluene-4-sulfonyl)-phenyl]-phosphane (1b)

To a solution of *p*-tolylsulfone (4.8 g, 19.5 mmol) in THF (50 mL) at −40 °C was added *n*-BuLi (8.6 mL of a 2.5 M solution in hexanes, 21.5 mmol). The reaction mixture was warmed to −20 °C and stirred for 2 h. Dicyclohexylchlorophosphine (5 g, 21.5 mmol) was added and the reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated sodium bicarbonate solution (25 mL) and the resulting mixture was extracted with dichloromethane (100 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was reslurried in isopropanol (90 mL) and provided pure **1b** as a white solid (5.5 g, 64%).

1.2. 2-Dicyclohexylphosphanyl-1-trityl-1*H*-imidazole (2a)

To a solution of trityl imidazole (6.06 g, 19.5 mmol) in THF (60 mL) at −40 °C was added *n*-BuLi (8.6 mL of a 2.5 M solution in hexanes, 21.5 mmol). The reaction mixture was warmed to −20 °C and stirred for 2 h. Dicyclohexylchlorophosphine (5 g, 21.5 mmol) was added and the reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated sodium bicarbonate solution (25 mL) and the resulting mixture was extracted with dichloromethane (100 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was reslurried in isopropanol (60 mL) and provided pure **2a** as a white solid (5.04 g, 51%).

1.3. Dicyclohexyl-[2-(1-phenyl-vinyl)-phenyl]-phosphane (3)

2-Bomobenzophenone (9.50 g, 36.4 mmol) was added to the Petasis reagent (150 mL of a 0.48 M solution in toluene, 72.7 mmol) and heated at 80 °C for 12 h. The reaction was cooled to room temperature and isopropyl ether (95 mL) was added. The yellow slurry was stirred for 30 min and the solids were then removed by filtration over Celite. The mother liquor was then concentrated and purified by column chromatography (99:1 hexanes/triethylamine) to provide the *exo*-olefin as a clear and colorless oil (7 g, 74%).

A solution of the *exo*-olefin (7.0 g, 27.0 mmol) in THF (70 mL) was cooled to −78 °C and *n*-BuLi (12 mL of a 2.5 M solution in hexanes, 29.9 mmol) was added. The resultant solution was then stirred at −78 °C for 30 min and quenched with chlorodicyclohexylphosphine (7.25 mL, 32.6 mmol). The reaction was allowed to slowly warmed to room temperature and then was quenched with water (70 mL) and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude product was reslurried in ethanol (7 mL) to afford **3** as a white solid (5.5 g, 54%).

1.4. General preparation for the catalytic amination of aryl bromides

A solution of palladium acetate (14 mg, 62 μmol) and the ligand (74 μmol) in toluene (2.5 mL) was sparged with nitrogen for 15 min. The aryl halide (1.24 mmol), the amine (1.49 mmol), and the base, either sodium *t*-butoxide or cesium carbonate (1.61 mmol) was added and the resultant reaction mixture was heated at 100 °C for 2–24 h (reaction times were not minimized). The reaction was cooled to room temperature, quenched with water (15 mL), and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The material was purified via column chromatography on silica gel typically using a mixture of ethyl acetate and hexanes as eluent.

References and notes

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