Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates

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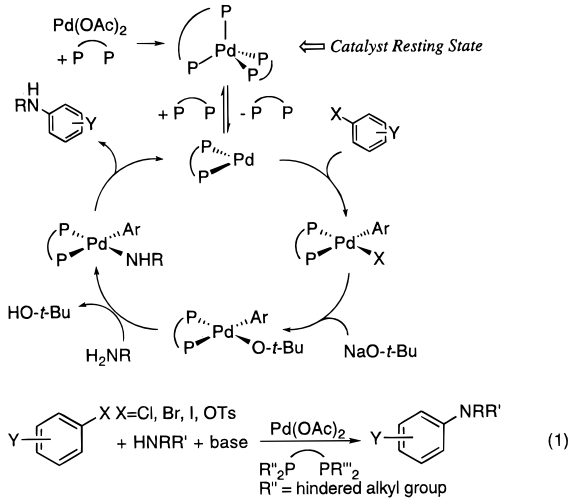
Aromatic phosphines and arsines are typically used as ligands in synthetically valuable palladium-catalyzed cross-coupling processes that include recently developed couplings to form arylamines and aryl ethers from aryl halides and triflates.[1−3] We have recently sought palladium systems comprised of air stable components that provide faster reaction rates for aryl bromide and iodide amination and allow the amination of less activated and commercially important aromatic substrates such as aryl chlorides and tosylates. Using a mechanistic rationale for the choice of ligands, these goals have now been achieved with sterically hindered chelating alkyl phosphine ligands.[4,5]

Because our group and Buchwald's have recently showed that chelating phosphine ligands containing aromatic substituents give high selectivity for the amination of aryl halides with primary amines,[6,7] our studies toward rate acceleration focused on chelating ligands. Mechanistic data[8−12] on the aryl halide amination reactions catalyzed DPPF (1,1′-bis(diphenylphosphino)ferrocene) or BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) palladium compounds support the mechanism in Scheme 1.

Our studies on rate enhancement began with ^{31}P NMR spectroscopic studies to reveal the dominant form of the catalyst in solution. Reactions between *o*-tolyl or *p*-tolyl bromide and *n*-butylamine in the presence of NaO-*t*-Bu were conducted with 20 mol % of several catalysts, including [Pd(BINAP)$_2$], [Pd(DPPF)$_2$], [Pd(OAc)$_2$] with either 1.5 equiv of BINAP or DPPF, and [Pd(DBA)$_2$] with 1.5 equiv of DPPF. In all cases, the species observed at 80 °C by ^{31}P NMR spectroscopy was Pd(0)L$_2$ (L = BINAP or DPPF).[13] Thus, oxidative addition of aryl bromide is the likely rate-determining step for the amination reactions catalyzed by DPPF- or BINAP-ligated palladium and more active catalysts must increase the rate of this step.

Increasing the electron density at the metal center by employing chelating alkyl, rather than aryl, phosphine ligands may accelerate reaction rates. However, we have recently shown that oxidative addition involves complete dissociation of one of the chelating phosphine ligands to produce a bent Pd(0) chelate complex.[14] Thus, tight binding of alkyl phosphines might, in fact, decelerate the oxidative addition by disfavoring dissociation that generates the active bent Pd(0)L. We, therefore, reasoned that sterically hindered alkylphosphine ligands might provide the required electron rich metal center, while favoring ligand dissociation.

Scheme 1



For these reasons we tested the known, but infrequently studied, ligand DB^{t}PF (1,1′-bis(di-*tert*-butylphosphino)ferrocene)[15,16] (**1**) in the amination reactions. DB^{t}PF is readily prepared by dilithiation of ferrocene, followed by quenching with ClP(*t*-Bu)$_2$.[16] It is air sensitive over long periods of time in solution, but can be handled and weighed in air. Table 1 summarizes our results with this ligand and others discussed below in the general reaction presented in eq 1, and these results illustrate (1) remarkable rate enhancements for reactions with sterically hindered alkylphosphine ligands, (2) mild conditions for aminations of aryl chlorides, (3) the first amination of aryl tosylates, and (4) the first preparation of mixed alkyl arylamines in high yields by the metal-catalyzed amination of unactivated aryl chlorides with primary alkylamines. The functional group compatibility of palladium-catalyzed amination chemistry has been discussed previously.[17]

DB^{t}PF leads to exceptionally high-yield amination of unactivated aryl chlorides with aniline (entry 1). Reactions were complete after 1 day at 110 °C in toluene solvent, but were complete in only 4 h in dioxane solvent (entry 2). Entry 6 shows that this ligand allows for the palladium-catalyzed amination of aryl chlorides with primary alkylamines in acceptable yields. Diarylation[7,18] and competing hydrodehalogenation are assumed to be competing reactions in this case. Entries 11 and 12 show that this ligand provides excellent yields of dialkyl anilines from unactivated aryl chlorides under much milder conditions than previous palladium-catalyzed chemistry with unactivated chloroarenes.[4] Previous unpublished work in our laboratory showed that palladium complexes of 1,1′-bis(dimethylphosphino)ferrocene were ineffective catalysts for the amination chemistry. This result, in combination with those reported here, shows the importance of ligand steric hindrance.

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(13) The fate of the remaining palladium in cases where 1.5 equiv of ligand was added to a catalyst precursor is unclear at this time. However, Pd(OAc)$_2$ did not catalyze amination, demonstrating that the catalyst is the phosphine-ligated complex.
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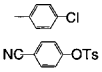
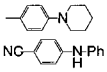
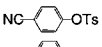
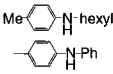
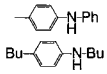
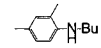
Table 1. Hindered, Chelating Alkylphosphines in the Amination of Aryl Halides and Tosylates[a]

	Amine	ArX	Product	Catalyst	Conditions	Yield[b]
1	NH_2Ph			3 mol% Pd(dba)/**1**	110 °C, 24 h	93%
2	"			3 mol% Pd(dba)/**1**	110 °C, 4	93%[c]
3	"			2 mol% Pd(dba)/**2**	110 °C, 16 h	99%
4	"			1 mol% Pd(OAc)/**2**	85 °C, 12h	92%
5	"			2 mol% Pd(dba)/**3**	110 °C, 16 h	96%
6	NH_2Bu			1 mol% Pd(dba)/**1**	110 °C, 24 h	57%
7	"			1 mol% Pd(OAc)/**2**	85 °C, 2 h	89%
8	"			1 mol% Pd(OAc)/**3**	85 °C, 2 h	94%
9	NH_2Bu			1 mol% Pd(OAc)/**2**	85 °C, 2 h	89%
10	"			1 mol% Pd(OAc)/**3**	85 °C, 12 h	87%
11				1 mol% Pd(OAc)/**1**	100 °C, 10 h	81%
12				1 mol% Pd(OAc)/**1**	100 °C, 12 h	85%
13	NH_2Ph			2 mol% Pd(dba)$_2$/**1**	110 °C, 16 h	79%
14	NH_2hexyl			2 mol% Pd(OAc)$_2$/**2**	110 °C, 2 h	83%[d]
15				5 mol% Pd(dba)$_2$/**1**	r. t., 20 h	94%
16	NH_2Bu			1 mol% Pd(dba)$_2$/**1**	r. t., 24 h	47%
17	NH_2Bu			1 mol% Pd(dba)$_2$/**1**	r. t., 7 h	49%
18	NH_2Ph			1 mol% Pd(dba)$_2$/**1**	r. t., 24 h	95%

[a] Procedures: 1.0 equiv of aryl halide, 1.2 equiv of amine, and 1.2 equiv of NaO^{t}Bu were used along with the specified catalyst in toluene solvent. [b] Yields are for isolated product of >95% purity and are an average of at least 2 runs on a 1 mmol scale with 0.5−1.0 M concentrations. [c] Reaction run in dioxane solvent. [d] $NaOC_6H_3$-2,4,6-tBu used as base.

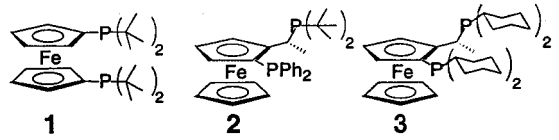


Figure 1. Ligands employed in the examples of Table 1.

Table 2. Effect of Ligand on Monoarylation vs Diarylation Selectivity for 4-Chlorotoluene and *n*-Butylamine

ligand	amine (H_2NR)	$HNArR:NAr_2R$
1	R = Bu	3.3:1
2	R = Bu	130:1
3	R = Bu	30:1
2	R = Ph	diarylation product not detected

Other chelating ligands with large bite angles created by backbones that are stable to basic conditions, while containing bulky alkyl substituents at the phosphorus, include ligand **2** in Figure 1 used by Lonza for the stereoselective reduction of biotin,[19] and related systems including **3** in Figure 1 reported by Togni et al. for asymmetric hydrogenation.[20,21] These ligands induced aminations of unactivated aryl chlorides with primary amines under remarkably mild conditions. The ligands **2** and **3** in Figure 1 were evaluated for the amination of hindered and unhindered aryl chlorides with aniline and butylamine. High yields of aryl chloride amination were observed with aniline (entries 3−5). The reaction in entry 4 that employs palladium acetate as catalyst precursor occurs under conditions reminiscent of previous aminations of aryl bromides. Table 2 shows that no diarylation of aniline was observed when ligand **2** was used.

In addition, high yields of mixed alkyl arylamines were obtained by employing these two ligands. Isolated yields between 87% and 94% were obtained when ligand **2** or **3** was used with palladium acetate at only 85 °C for 2−12 h for either hindered or unhindered aryl chlorides. Palladium precursors and ligands **2** and **3** catalyzed the amination of secondary amines only slowly, perhaps due to the exquisite selectivity for monoarylation, as shown in Table 2.[7] More rapid arylation of secondary amines was observed with **1** in combination of $Pd(OAc)_2$ providing an excellent catalyst for the arylation of secondary amines as discussed above.

Previous studies on the Pd-catalyzed amination of aryl chlorides using monodentate alkylphosphines required activated aryl chlorides and were limited to secondary amines.[22,23] Activation of chloroarenes by nickel is well established and Ni-catalyzed amination of aryl chlorides has been reported.[24] The work here shows that palladium-catalyzed chemistry, which is often less air sensitive and more general than that of nickel, can lead to amination of unactivated aryl chlorides in toluene solvent and with primary alkylamines.

Entries 13 and 14 show that hindered, chelating alkylphosphine ligands also generate effective catalysts for the amination of aryl tosylates. The reaction yields with unactivated aryl tosylates are remarkable, considering that little palladium-catalyzed cross-coupling with any type of aryl arene sulfonate has been reported.[25,26] These results illustrate the potential of using chelating alkyl phosphines in chemistry to convert phenols to amines with tosyl chloride instead of triflic anhydride to activate the phenol.

Ligand **1** allowed for aminations of aryl bromides with aniline in excellent yield at room temperature (entry 15). Previous room-temperature palladium-catalyzed amination chemistry required aryl iodides and the addition of crown ethers,[27] and aminations with aniline substrates required heating. Entries 16−18 show the room-temperature amination of aryl iodides without additives. In all cases complete consumption of the aryl iodide occurred before 24 h had elapsed. Yields for the amination of aryl iodides with primary alkylamines were acceptable. However, the yields for amination of the unactivated aryl iodide in entry 19 with primary arylamines were excellent.

Our previous studies on the reductive elimination of diarylamine from (DPPF)Pd(Ar)(NHAr) complexes showed that this primary reaction required several hours at room temperature.[8] We expected the presence of an alkylphosphine ligand to decelerate the reductive elimination of diarylamine, preventing room-temperature chemistry with aniline. Perhaps the size of the DB^t-PF ligand compensates for the increased electron density at the metal, maintaining fast rates for reductive elimination.

A general problem in catalysis involves identifying systems that are rapid at both activating and extruding organic molecules. By using sterically hindered alkyl phosphines, it appears that both oxidative addition and reductive elimination are accelerated. This proposal will be tested in future mechanistic work that will accompany studies with dialkylphosphino ligands containing different backbones and the use of these ligands in the α-arylation of ketones and amides.

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Supporting Information Available: Reaction procedures and spectroscopic data of ligands and reaction products (7 pages, print/PDF). See any current masthead page for ordering and Web access instructions. instructions.

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