Amination

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Monodentate Phosphines Provide Highly Active Catalysts for Pd-Catalyzed C–N Bond-Forming Reactions of Heteroaromatic Halides/Amines and (H)N-Heterocycles**

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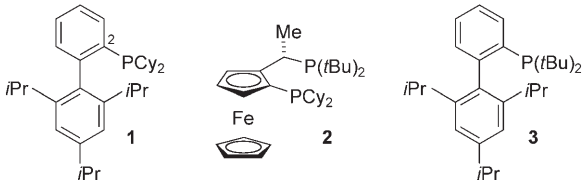
Despite advances in the scope of palladium-catalyzed C–N bond-forming reactions through the development of more active catalysts,[1,2] limitations to the method still remain: 1) In many cases the coupling of substituted heteroaryl halides with amines is still problematic; 2) the N-arylation reactions of nitrogen heterocycles is limited in scope with respect to both coupling partners; 3) chemoselectivity in C–N bond-forming processes has not been explored in great detail.

Palladium catalysts based on dialkylphosphinobiaryl ligands[1b,3] have not only been shown to display high stability, but also have manifested increased reactivity in palladium-catalyzed carbon–carbon,[4] carbon–nitrogen,[1b,3] and carbon–oxygen[1b,5] bond-forming reactions. Our previous studies indicated that a catalyst system based on Pd/2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos; **1**; Cy = cyclohexyl) demonstrated both a greater degree of activity and stability than those derived from our previous generations of ligands.[6] The substitution of the 2′,2′-positions on the lower aromatic ring prevents palladacycle formation,[7] and the added bulk causes the equilibrium to shift from that favoring [L_2Pd^0] to one in which [L_1Pd^0] predominates, thus facilitating all steps in the catalytic cycle.[7–10]



Recently, a long-lived catalyst based on the combination of a Pd precatalyst and bidentate Josiphos-type ligand **2** was shown to provide good results for the coupling of highly functionalized aryl/heteroaryl chlorides and primary amines.[11] It was postulated that the high reactivity of the system was, to a significant extent, as a result of the tight chelation of **2** to the Pd center, thus decreasing the chance for the binding of a heterocycle or basic amine, which may facilitate the loss of the ligand or otherwise deactivate the catalyst. Although this is an extremely reasonable supposition, we wondered whether, in fact, the use of chelating ligands was necessary for successful reactions with substrates of this type. Herein, we report our results which indicate that monodentate phosphines are viable alternatives to and are sometimes superior to chelating ligands in Pd-catalyzed C–N bond-forming processes.

We first explored the coupling of 4-chlorophenol and *n*-hexylamine (Table 1). Ligand **1** proved to be ineffective for this reaction, with its use resulting in incomplete conversion and lower yields as a result of diarylation (Table 1, entries 1 and 2). Interestingly, we found that the combination of **3** as the ligand and lithium hexamethyldisilazide (LiHMDS)[12] as the base was the most effective for this transformation at 50 °C, thus providing the product in 94 % yield in 2 h (Table 1, entry 6). This system is also proficient at room temperature, as the aryl amine is provided in 94 % yield, although the reaction required 46 h to go to completion (Table 1, entry 4). While Josiphos-type ligand **2** was reported to perform well at 100 °C for a similar transformation, its efficiency was far less than **3** at 40 °C (Table 1, compare entry 3 vs entry 5).

We previously disclosed that a catalyst system comprised of a Pd precatalyst and **1** displayed excellent chemoselectivity for reaction at an aniline NH_2 group over that of a primary amide.[6a] We have found that use of [$Pd_2(dba)_3$]/**1** (dba = dibenzylideneacetone) and LiHMDS allows the reaction of aliphatic primary and cyclic secondary amines with a substrate containing a primary amide (3-chlorobenzamide), which has been problematic with previous catalyst systems

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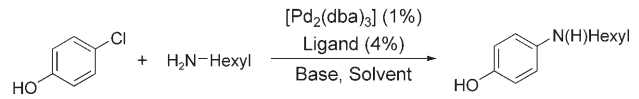
Table 1: Ligands used for the coupling of 4-chlorophenol and *n*-hexylamine.



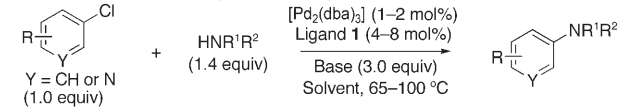
Entry	Ligand	Base	Solvent	*T* [°C]	*t* [h]	Conv. [%]	Yield [%][a]
1	**1**	$LiN(TMS)_2$	THF	40	24	84	31[b]
2	**1**	NaO*t*Bu	toluene	100	24	44	15[b]
3[c]	**2**	$LiN(TMS)_2$	THF	40	24	17	2[b]
4	**3**	$LiN(TMS)_2$	THF	RT	46	>99	94
5	**3**	$LiN(TMS)_2$	THF	40	24	>99	94
6	**3**	$LiN(TMS)_2$	toluene	50	2	>99	94
7	**3**	NaO*t*Bu	toluene	100	24	>99	89

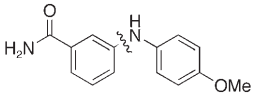
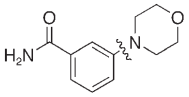
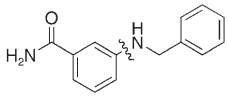
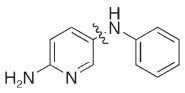
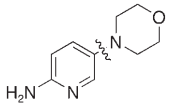
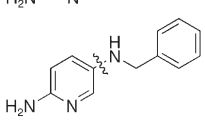
[a] Yield of the isolated product. [b] Yield determined by GC analysis. [c] Reagents and condition: ligand **2**, octylamine, $LiN(TMS)_2$, 1,4-dioxane, 100 °C; yield = 72 %.[11] TMS = trimethylsilyl.

(Table 2).[12] 2-Aminohaloheterocycles have previously been inefficient electrophilic components for C–N bond-forming processes with monophosphine ligands. Thus, we examined the coupling of 2-amino-5-chloropyridine with aniline and morpholine (with **1**) and benzylamine (with **3**) and were pleased to find that these reactions proceeded in good yield.

The use of 2-aminoheterocycles as a nucleophilic component had only successfully been accomplished with aryl bromides utilizing a Pd/XantPhos[13] or binaphthol (BINAP)[14] catalyst system. A common belief is that using a bidentate ligand would prevent any coordination to a Pd^{II} species of the "guanidine-like" moiety of these substrates. Thus, the discovery that a catalyst comprised of $[Pd_2(dba)_3]$ and **3** was effective in the N-arylation of 2-aminopyridine was somewhat surprising. We explored the use of Pd/**3** for a diverse array of reaction combinations.[15] Substrates bearing a free hydroxy and indole –NH group react well with 2-aminopyridine and 2-aminopyrimidine, respectively, providing 92 and 57 % of the resultant diaryl amines (Table 3). In accord with the previous results, reaction at the heteroaromatic $-NH_2$ group prevails over that at a primary amide and provides 94 % yield in the coupling of 5-bromonicotinamide and 2-aminopyridine.[15]

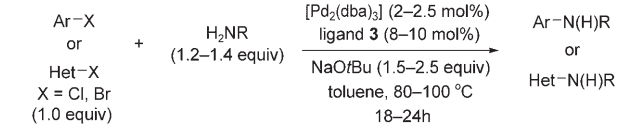
Table 2: Chemoselectivity in Pd-catalyzed amination.

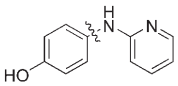
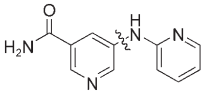
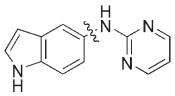
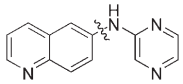
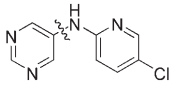
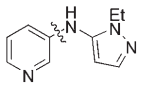


Product	Yield [%]
	79[a,b] 82[a,c]
	81[d]
	83[d]
	89[d]
	79[d]
	77[d,e]

[a] Previously reported, see Ref. [6a]. [b] K_2CO_3 in *t*BuOH, 100 °C, 20 h. [c] NaO*t*Bu in toluene, 100 °C, 18 h. [d] $LiN(TMS)_2$ in THF, 65 °C, 16–24 h. [e] Ligand **3** was used.

Table 3: Palladium-catalyzed N-arylation of aminoheterocycles.



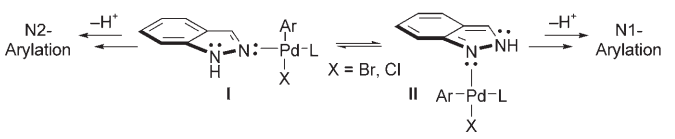
Product	X	Yield [%]
	Cl	92
	Br	94
	Br	57[a]
	Cl	60[a]
	Br	75
	Cl	74[b]

[a] Cs_2CO_3 and *N*,*N*-dimethylformamide used as base and solvent, respectively. [b] 1,4-Dioxane used as solvent.

Prior work on the N-arylation of indoles and pyrroles revealed that catalytic systems based on monophosphinobiaryl ligands were somewhat effective.[16] In contrast, more acidic heterocycles, such as indazole or pyrazole, have not been reported to be coupling partners in palladium-based methods. Given our success with the Pd/**3** combination for the coupling of less basic 2-aminoheterocycles (Table 3), we felt that it might also be quite effective for the coupling of these nitrogen heterocycles. Indazole/pyrazole are expected to be less basic than their indole/pyrrole counterparts,[17] thus a more bulky phosphine moiety might speed up reductive elimination from a Pd aryl/amido intermediate.[18]

We first explored the N-arylation of indazole with 3-bromoanisole using Pd/**3** with K_3PO_4 in 1,4-dioxane at 100 °C. This system provided 52 % conversion and 48 % yield (GC) of the N1-arylated product exclusively; a result which is also

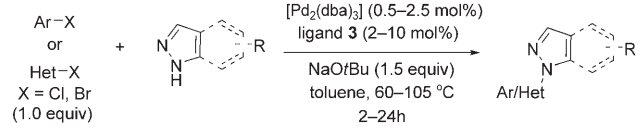
observed for the coupling of aryl iodides using Cu-catalysis methodology.[19] Optimization of the reaction conditions revealed that use of the bases NaO*t*Bu (toluene, 80 °C) and Cs_2CO_3 (1,4-dioxane, 105 °C) provided the N1-arylated indazole in excellent yields using $[Pd_2(dba)_3]$/**3**. Interestingly, when NaO*t*Bu is used as the base at 100 °C, mixtures of the N1- and N2-arylated products were observed. One explanation for this result is that **I** (Scheme 1) is the kinetically



Scheme 1. Hypothesis for chemoselectivity in the N-arylation of indazole.

formed species (binding at the lone pair of electrons on N1 would disrupt the aromaticity, **I'**). At 80 °C (with NaO*t*Bu) or 105 °C with Cs_2CO_3, conversion into **II** occurs faster than deprotonation. As is seen in Table 4, indazole is arylated with

Table 4: Palladium-catalyzed N-arylation of indazole and pyrazole.



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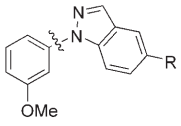
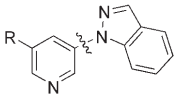
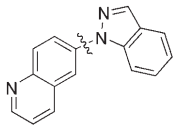
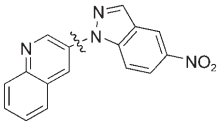
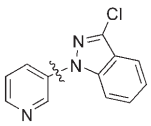
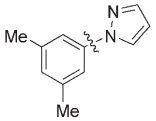
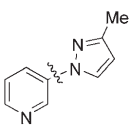
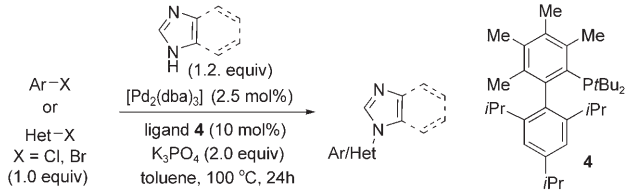
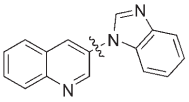
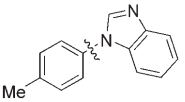
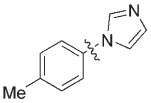
	H	Cl	80	97
	NO_2	Br	80	91
	H	Cl	80	97
	CN	Br	60	62
	–	Cl	80	99
	–	Br	90	92
	–	Br	60	79
	–	Br	80	88
	–	Cl	105	76

3-chloroanisole, 3-chloropyridine, 5-bromonicotinonitrile, and 6-chloroquinoline in respectable yields. Also, 5-nitroindazole is effectively treated with 3-bromoanisole and 3-bromoquinoline, thus providing the N-arylated heterocycles in 93 and 89% yields, respectively. Further, for the first time, pyrazole is efficiently combined with an aryl bromide and aryl chloride using a palladium catalyst.

To our knowledge, palladium-catalyzed amination reactions of benzimidazole and/or imidazole with unactivated aryl halides have not been accomplished.[20] As is seen in Table 5, the use of the especially hindered ligand **4** facilitates C–N bond-formation of these weakly basic nitrogen nucleophiles. Benzimidazole is coupled with 3-bromoquinoline and 4-chlorotoluene and provides the

Table 5: Palladium-catalyzed *N*-arylation of imidazole and benzimidazole.



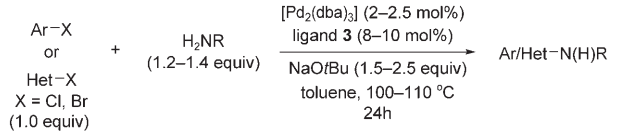
Product	X	Yield [%]
	Br	94
	Cl	97
	Br	70[a]

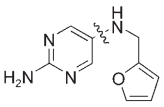
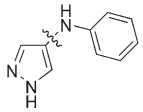
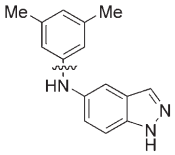
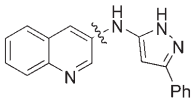
[a] With *N*,*N*-dimethylaniline used as solvent.

N-arylated products in 94 and 97% yields, respectively (Table 5). Imidazole is combined with 4-bromotoluene in a 70% yield, thus representing the first known palladium-catalyzed example of this coupling with an unactivated aryl bromide. Here the use of **4** may be necessary to facilitate the rate of reductive elimination from a $[L_1Pd(Ar)(N\text{-}Het)]$ intermediate.[21]

We have also explored the coupling of some amino-heterocycles and/or pyrazole substrates (Table 6). The results that we have obtained, in some cases, complement those previously seen with Cu-catalyzed protocols. The chemoselectivity of the aniline NH_2 group causes it to react in preference to the indazole –NH group, thus providing a 67% yield in the reaction of 5-aminoindazole with 5-bromo-*m*-xylene. We were particularly surprised to find that 5-amino-3-phenylpyrazole could be selectively arylated at the primary amino group, which is the first time, to our knowledge, that an unprotected aminopyrazole has ever reacted with this mode

Table 6: Interesting chemoselectivity in palladium-catalyzed C–N bond formation.



Product	Yield [%]	Product	Yield [%]
	72		94
	67		88

of chemoselectivity in a metal-catalyzed C–N bond-forming process. For example, we have previously shown with Cu catalysts that aminopyrazoles react preferentially at the pyrazole –NH group, thus representing complementarity between the Pd- and Cu-based methods.[19] Finally, for the first time a free (H)N-bromopyrazole can be successfully aminated, in this case with aniline as shown.

In conclusion, we have developed highly reactive catalysts based on palladium and dialkylbiarylphosphino ligands, particularly **1**, **3**, or **4**. These provide unprecedented reactivity and selectivity in C–N bond-forming processes. The bulky monophosphine catalyst system Pd/**1** was effective for the reaction of aryl/heteroaryl halides bearing primary amides and 2-aminoheterocycles. Also, the more sterically encumbered catalyst systems based on Pd and ligands **3** or **4** were found to be more proficient for the arylation of 2-aminoheterocycles and weakly basic HN heterocycles: pyrazoles, indazole, benzimidazole, and imidazole. The chemoselectivity of these catalysts was explored and the rough order of reactivity for amines follows the general trend: aryl amines $\gg$ primary and secondary aliphatic amines $>$ 2-aminoheteroaromatics $>$ primary amides $\approx$ HN heterocycles. We hypothesize that the efficacy of palladium catalysts based on ligands **1**, **3**, or **4** is attributed to a combination of factors: 1) A maximization of the amount of L_1Pd intermediates, thus speeding the desired catalytic process relative to different modes of catalyst decomposition; 2) providing quasi-stable [L_1Pd], [$L_1Pd(Ar)X$], and [$L_1Pd(Ar)$amido] intermediates because the size of these complexes slows bimolecular decomposition processes and because of stabilizing Pd/arene interactions; 3) providing [$L_1Pd(Ar)$amido] intermediates with especially sterically demanding ligand L_1 facilitates the rate of reductive elimination in forming the product. Further, this study demonstrates that monodentate ligands are viable alternatives to and sometimes superior to chelating ligands in Pd-catalyzed C–N bond-forming processes.

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