Amination

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Electronic Effects on the Selectivity of Pd-Catalyzed C–N Bond-Forming Reactions Using Biarylphosphine Ligands: The Competitive Roles of Amine Binding and Acidity**

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Dedicated to Süd-Chemie on the occasion of its 150th anniversary

In 2003, we reported that aniline derivatives could be selectively coupled to aryl halides in the presence of aliphatic amines using Pd catalysts with biarylphosphine ligands[1]—chemoselectivity that was not well-understood at the time.[2] To clarify the origin of this selectivity, we have studied the formation of amine complexes using an aryl palladium oxidative addition complex recently reported by our lab.[3] From these studies, we have isolated and characterized the first neutral aryl palladium amine complex that is a competent intermediate in a C–N cross-coupling reaction. For various amines, we have determined the relative binding constants to the oxidative addition complex and described how selectivity in the catalytic arylation of amines is influenced by the electronic properties of the amine. Additionally, we have shown how selectivities observed in C–N cross-coupling reactions using neutral amines can be reversed through use of the corresponding lithium amides.

The preparation of oxidative addition (**1**) and amine (**2**) complexes using 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPhos) is illustrated in Figure 1.[4] Complex **1**, formed from PhCl and [SPhosPd^0], exists in the solid state as a dimer with bridging chloride ligands (see the Supporting Information).[3] The addition of propylamine to **1** results in the formation of amine complex **2**, which is monomeric. Complexes **1** and **2** are both chemically and kinetically competent intermediates in the formation of *N*-propylaniline.

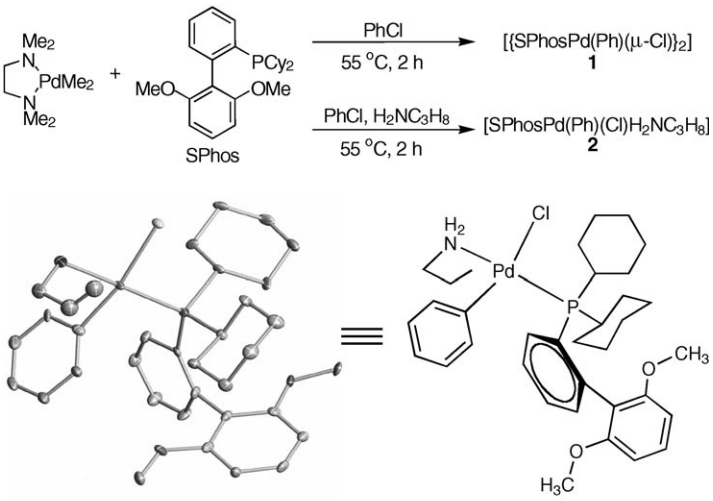
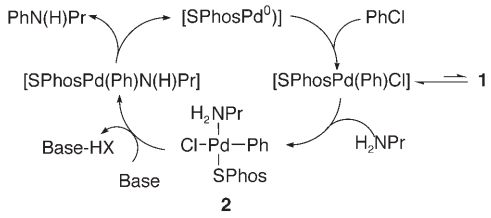


Figure 1. Synthesis of complexes **1** and **2**. X-ray crystal structure of **2** (thermal ellipsoids at 30% probability).

Complex **2** is the first isolated and structurally characterized example of a free amine bound to {LPd(Ar)X} (L = monophosphine), a presumed intermediate in the Pd-catalyzed aryl amination process (Scheme 1).[5] As expected, the



Scheme 1. Catalytic cycle for the phenylation of H_2NPr using SPhos.

N–Pd bond length of **2** (2.14 Å) is longer than those observed in tricoordinate monoligated amido complexes (2.07–2.09 Å).[6] An additional noteworthy feature of the X-ray structure of **2** is the positioning of the lower (non-phosphine-containing) aryl ring of SPhos away from the palladium center. Calculations and NMR spectroscopy experiments have shown that the monomer of **1** interconverts between a species where the *ipso* carbon of the lower aryl ring is coordinated to the palladium center and a species where a methoxy group is coordinated to the palladium center.[3]

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

These results are consistent with C_{aryl}–P bond rotation before or concurrent with the binding of the amine. Thus, we have obtained structural evidence that suggests that the ability of the ligand to undergo C_{aryl}–P bond rotation will likely have profound effects on the reactivity of the associated palladium complex. This influence has been previously suggested by our group through the use of DFT calculations for amidation reactions.[7]

Complex **1** was treated with various amines to evaluate their relative binding affinities to oxidative addition complexes within a catalytic cycle. Figure 2 shows the ^{31}P NMR spectra that result from the addition of Bu_2NH (Figure 2a) and aniline (Figure 2b) to **1** in separate reactions. In each spectrum, a signal corresponding to the amine complex is visible, and no evidence of **1** remains. Upon combining 1.2 equivalents of both Bu_2NH and aniline with **1** (Figure 2c), it is clear from the ^{31}P NMR spectrum that Bu_2NH exhibits a much greater binding affinity; no evidence of aniline binding is observed. However, when NaO*t*Am (*t*Am = 1,1-dimethylpropyl) is added to the NMR tube, diphenylamine is the only product observed. These data suggest that the process is under Curtin–Hammett (C–H) control, for which the nominal contributor to the dynamic equilibrium between **3** and **4** is most reactive.[8]

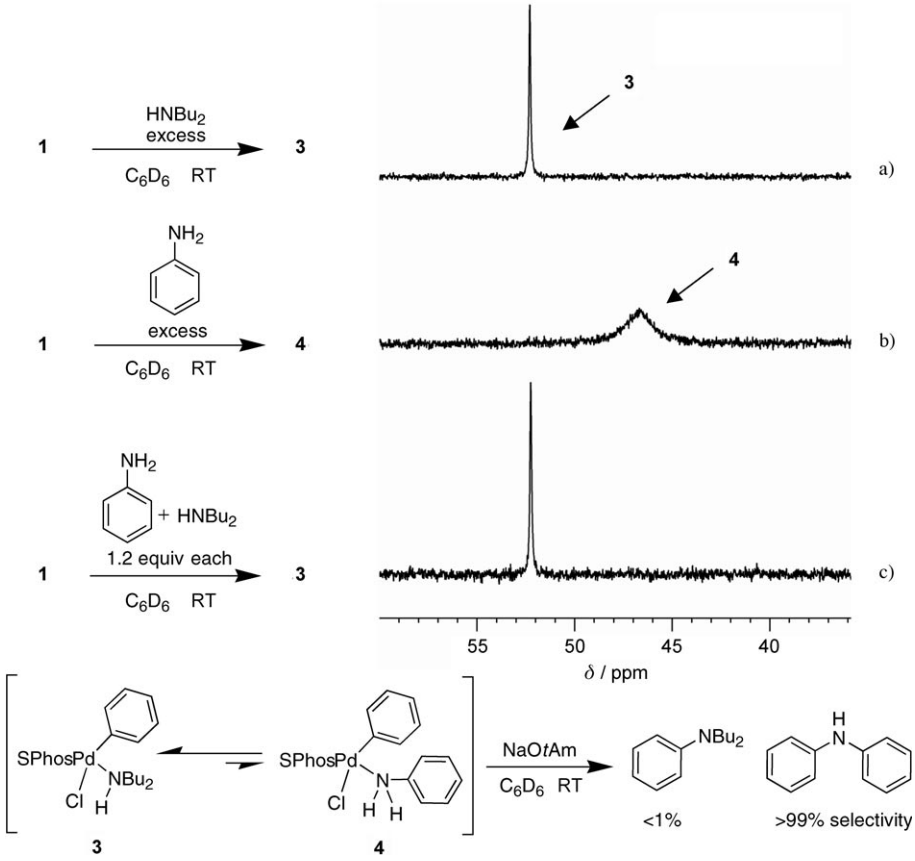
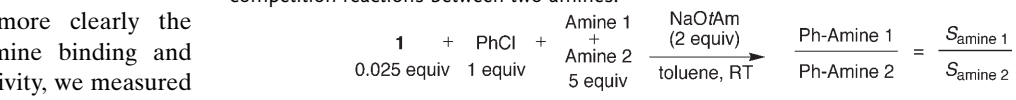


Figure 2. ^{31}P{^{1}H} NMR spectra of **1** with a) excess dibutylamine, b) excess aniline, and c) 1.2 equiv of dibutylamine and aniline.

To define more clearly the influence of amine binding and acidity on selectivity, we measured the relative binding affinity of a series of amines to **1**, thus correlating binding and acidity to the selectivity obtained in competitive catalytic cross-coupling reactions with PhCl. Binding constants are presented in Table 1 and listed relative to morpholine.[9] The absolute $K_{binding}$ for aniline was determined to be $(3.39 \pm 0.08)\,\text{M}^{-1}$, from which other absolute binding constants can be extrapolated.[10]

To conduct competition reactions under catalytic conditions, **1** was employed as a precatalyst. In Table 1, the ratio of selectivity values (*S*) for two amines represents the relative selectivity observed in catalytic competition reactions with PhCl using precatalyst **1**. From comparisons of relative binding constants, pK_a values, and *S* values within the series of amines, it is clear that a separate correlation of

Table 1: Relative binding constants of different amines to complex **1** and selectivies observed in competition reactions between two amines.



Entry	Amine	$K_{binding\ (rel)}$[a]	ΔG_b [kcal mol^{-1}]	pK_a[b]	S[a,c,d]
1	$C_6H_5NH_2$	0.004 ± 0.001	3.27 ± 0.17	4.60	9.37(9.42)[e]
2	*p*-$MeC_6H_4NH_2$	0.010 ± 0.003	2.72 ± 0.22	5.07	11.1
3	*p*-$MeOC_6H_4NH_2$	0.032 ± 0.002	2.04 ± 0.04	5.34	13.4
4	*p*-$Me_2NC_6H_4NH_2$	0.057 ± 0.006	1.70 ± 0.06	6.08	14.6
5	$(MeOCH_2CH_2)_2NH$	0.28 ± 0.02	0.75 ± 0.05	8.51[f]	0.034
6	Bu_2NH	1.94 ± 0.02	-0.39 ± 0.01	11.25	0.016
7	*N*-Boc piperazine[g]	0.83 ± 0.02	0.11 ± 0.01	8.28	1.22
8	morpholine	1.00	0.00	8.36	1.00
9	piperidine	5.32 ± 0.09	-0.99 ± 0.01	11.22	0.667
10	*t*$BuNH_2$	0.29 ± 0.01	0.73 ± 0.02	10.55	0.001
11	*s*$BuNH_2$	3.29 ± 0.07	-0.71 ± 0.01	10.56	0.262

[a] Average of two measurements. [b] pK_a values (in H_2O) taken from ref. [11a–d]. [c] *S* values relative to morpholine [d] Determined by GC. [e] Conducted at 100 °C using Cs_2CO_3 as base. [f] pK_a value estimated using ref. [11d] [g] Boc = *tert*-butyloxycarbonyl.

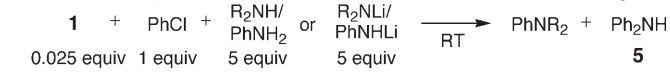
binding and acidity to selectivity exists within the series of anilines (Table 1, entries 1–4) and within the series of aliphatic amines (Table 1, entries 5–11). Within the series of aliphatic amines, the relative acidity of the amine complex has more influence on the observed selectivity than the relative binding affinity of the amine. This trend can be observed by comparing groups of isosteric aliphatic amines (Table 1, entries 5 and 6 or 7–9). When the butyl groups of dibutylamine are replaced with methoxyethyl groups (Table 1, entries 5 and 6), selectivity is increased more than two-fold owing to enhanced acidity, despite a seven-fold decrease in binding ability. When electron-withdrawing groups are inserted into the backbone of piperidine (Table 1, entries 7–9), greater selectivity is likewise observed for the more electron-deficient (lower pK_a)[11,12] amine, despite a necessary decrease in binding ability. Such electronic control is also observed when an aliphatic amine competes against an aniline derivative, as the coupling is invariably more selective for the more acidic, less nucleophilic aniline substrates. These results are all consistent with C–H control.

In contrast, within the aniline series, product determination appears to be governed by relative binding ability.[13] The *S* value is highest for *p*-$Me_2NC_6H_4NH_2$ (Table 1, entry 5), which binds the strongest. For anilines that are more electron-deficient than *p*-$Me_2NC_6H_4NH_2$, it appears that the effect of enhanced acidity gained from binding to palladium no longer outweighs the decreased binding affinity, and poorer selectivity results. Thus, selectivity within the aniline series does not seem to be under C–H control.

Finally, when amine binding differs on account of steric differences rather than pK_a differences, as with *s*$BuNH_2$ and *t*BuNH (Table 1, entries 10 and 11) or Bu_2NH and piperidine (Table 1, entries 6 and 9), arylation is more selective for the less sterically encumbered amine as a result of its greater binding affinity.[14–16]

To illustrate the important role that the deprotonation step plays in product determination, three competition reactions analogous to those of Table 1 were performed in which lithium amides were employed instead of neutral amines (Table 2). In each reaction, a dramatic reversal of selectivity from that of Table 1 was observed. For reactions involving lithium amides, the binding/deprotonation step is eliminated from the catalytic cycle, and selectivity is determined by the relative nucleophilicity and steric bulk of the lithium amides as well as by the solvent employed. The greater solubility of $LiNBu_2$ over LiN(H)Ph likely contributes to the complete chemoselectivity reversal observed in dioxane. In DME, where both lithium amides are completely soluble, steric and nucleophilic differences between the lithium amides likely influence the observed selectivity the most. Thus, in cases where the acidity of the amine complex determines the overall chemoselectivity, use of the corresponding pre-deprotonated lithium amide permits a reversal of chemoselectivity.

Table 2: Competition reactions of lithium amides with PhCl using **1**.[a]



	$PhNBu_2$	:	**5**	PhN⟨⟩O	:	**5**	PhN⟨⟩	:	**5**
$R_2NH/PhNH_2$[b]	<1	:	>99	9	:	91	6	:	94
$R_2NLi/PhNHLi$[c]	>99	:	<1	86	:	14	96	:	4
$R_2NLi/PhNHLi$[d]	72	:	28	95	:	5	88	:	12

[a] Ratios determined by GC. [b] NaO*t*Am, toluene. [c] Dioxane. [d] Dimethoxyethane (DME).

In conclusion, we have isolated and crystallographically characterized the first neutral aryl palladium amine complex (**2**) that is an intermediate within a catalytic cycle. Using complex **1**, we have shown that between isosteric aliphatic amines, amine acidity is the primary influence on the selectivity (C–H control), while between isosteric anilines, amine binding is more influential (no C–H control). When amine acidity has more influence on selectivity, the intrinsic selectivity can be circumvented by employing the corresponding lithium amides and removing the deprotonation step from the catalytic cycle. The trends established by correlating binding and nucleophilicity to selectivity demonstrate that the origin of amine selectivity cannot be explained simply by steric effects, and that electronic properties of the amines must also be considered. The information gathered from these studies provides insight both into the mechanism of C–N couplings using biaryl phosphines and into the feasibility of achieving chemoselective C–N cross-coupling reactions.

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The location of all hydrogen atoms was calculated. The refinement of 337 parameters using 7638 reflections and 0 restraints gave $R_1 = 0.0331$, $wR_2 = 0.1100$ ($I > 2\sigma(I)$), goodness of fit on $F^2 = 1.197$, $\Delta\rho_{max/min}{}^{-1} = 2.194/-0.316$ e Å^{-3}. Crystal data for **2**: $C_{105}H_{138}Cl_2N_2O_4P_2Pd_2$, crystals from toluene/pentane, $M_r = 1834.76$, $0.24 \times 0.19 \times 0.11$ mm^3, monoclinic, space group $P2(1)/c$, $a = 24.6844(12)$, $b = 23.1209(12)$, $c = 16.8097(8)$ Å, $\beta = 97.0540(10)°$, $V = 9521.1(8)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.488$ Mg m^{-3}, $T = 100(2)$ K, $F(000) = 4425$, $2\theta_{max} = 49.42°$, monochromated $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $\mu = 0.641$ mm^{-1}, Siemens Platform three-circle diffractometer equipped with a CCD detector, 142833 measured and 16216 independent reflections, $R_{int} = 0.0692$. Data processed using the program SAINT supplied by Siemens Industrial Automation, Inc., structure determination by direct methods (SHELXTL V6.10, G. M. Sheldrick, University of Göttingen, and Siemens Industrial Automation, Inc.), structure refined on F^2 by full matrix least-squares methods, absorption correction applied with SADABS. All non-hydrogen atoms were refined anisotropically. The location of all hydrogen atoms was calculated. The refinement of 876 parameters using 16216 reflections and 0 restraints gave $R_1 = 0.1493$, $wR_2 = 0.3355$ ($I > 2\sigma(I)$), goodness of fit on $F^2 = 1.342$, $\Delta\rho_{max/min}{}^{-1} = 2.031/-2.946$ e Å^{-3}. CCDC-655749 (**1**) and CCDC-655750 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[15] Preliminary calculations suggest that arylations are less selective for primary amines than for secondary amines because of reversible deprotonation and slow reductive elimination. See the Supporting Information for further details.

[16] Because we focus herein on the influence of electronic effects on selectivity, a through investigation of steric effects was not performed. A more comprehensive study of the influence of steric effects on selectivity will be reported elsewhere.

