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Palladium-Catalyzed C−N(sp^2) Bond Formation: *N*-Arylation of Aromatic and Unsaturated Nitrogen and the Reductive Elimination Chemistry of Palladium Azolyl and Methyleneamido Complexes

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Palladium-catalyzed biaryl and aryl-vinyl coupling reactions are a general and reliable synthetic tool,[1] in large part because C−C bond-forming reductive elimination that involves two unsaturated covalent ligands is rapid.[2] This type of reductive elimination is typically faster than reductive eliminations involving an alkyl group (Figure 1).[2] Palladium-catalyzed C−N couplings that form arylamines have recently emerged as useful methodology[3] even though the hybridization of the carbon and nitrogen involved in the reductive elimination step of the catalysis[3d−5] is similar to that of the carbons in alkyl−aryl couplings. In contrast, the palladium-catalyzed coupling to form the aryl−nitrogen bonds in *N*-aryl azoles has not been reported, and the *N*-arylation of imines has only recently been reported.[6] The relationship between reductive elimination rates for alkyl, aryl, and vinyl complexes has been studied extensively,[2] but the relationship between these relative rates and those for reductive elimination of related amido, azolyl, and methyleneamido complexes in Figure 1 is unknown. We report our results on a general palladium-catalyzed arylation of azoles and imines using DPPF-ligated palladium, along with organometallic chemistry that answers these questions about C−N bond-forming reductive eliminations involving unsaturated or aromatic nitrogen.

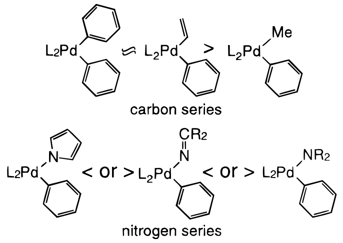
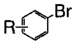
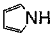
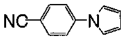
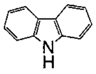
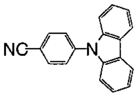
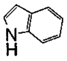
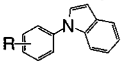
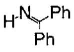
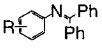
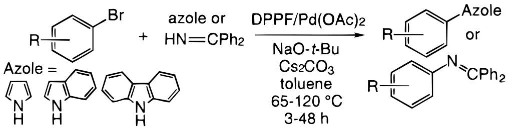


Figure 1. Relative rates for C−C bond formation by reductive elimination as a function of hybridization and the unknown relationships for C−N bond formation.

Table 1. Palladium-Catalyzed Arylation of Azoles and Benzophenone Imine

entry	Azole or Imine	 R=	Product	Method[a]	yield[b]
1		*p*-CN		A	92
2		*p*-*t*-Bu		B	87
3		*m*-OMe		B	74
4		*p*-CN		A	97
5		*p*-CN		A	98
6		*p*-C(O)H		A	76
7		*p*-CF_3		A	90[c]
8		*p*-Ph		A	72
9		*p*-C(O)NEt_2		A	85
10		*p*-H		B	78
11		*p*-CN		C	92
12		*o*-OMe		C	86
13		*o*-Me		C	90
14		*p*-OMe		C	93
15		*p*-C(O)Ph		C	90

[a] Procedures: A, 1.2 mmol ArBr, 1.0 mmol azole, 1.2 mmol Cs_2CO_3, 1 mol % $Pd(OAc)_2$, 1.5 mol % DPPF, 100 °C 12 h; B, 1.5 mmol ArBr, 1.0 mmol azole, 1.5 mmol NaO-*t*-Bu, 5.0 mol % $Pd(OAc)_2$, 6.0 mol % DPPF, 120 °C 48 h; C, 1.2 mmol ArBr, 1.0 mmol benzophenoneimine, 1.2 mmol NaO-*t*-Bu, 0.5 mol% $Pd(OAc)_2$, 0.75 mol % DPPF, 65-95 °C, 3-6h. Reactions were run in toluene solvent and the products were isolated by silica gel chromatography using hexanes and EtOAc. [b] Yields are for isolated pure material and are an average of at least two runs. [c] This material was formed in high yield, but was difficult to purify from small amounts of a side product. Yields by GC analysis are, therefore, reported.



(1)

Palladium-catalyzed coupling reactions that form *N*-aryl azoles and *N*-aryl imines by C−N(sp^2) bond formation are summarized in eq 1 and Table 1. *N*-Aryl imines are conveniently protected anilines.[6] *N*-Aryl azoles display a variety of biological activity.[7] Procedures for azole arylation are limited. Phenylation with electrophilic aromatic main group compounds deliver only one of several aryl groups,[8,9] KF adsorbed onto alumina mediates arylations of azoles with only electron-poor aryl halides,[10] and copper-mediated azole arylations require high temperatures and often toxic solvents.[11] This paper includes data on imine arylation using DPPF-ligated palladium in order to demonstrate the differences in rates on the arylation of different types of sp^2-hybridized nitrogen using the same catalyst.

The combination of $Pd(OAc)_2$ and DPPF catalyzed the formation of *N*-aryl azoles in the presence of Cs_2CO_3 or NaO-*t*-Bu with electron-rich, electron-neutral, or electron-poor aryl halides over the course of 12−48 h at 100−120 °C.[12] Complete reaction of electron-rich aryl halides required the higher temperatures and longer times. This process encompassed arylations of pyrrole, indole, and carbazole.

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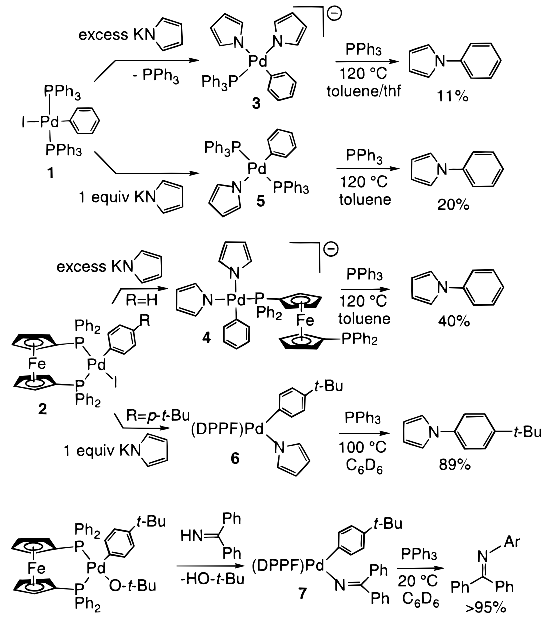
S0002-7863(97)03524-5 CCC: $15.00

Scheme 1



The palladium-catalyzed arylations of imines with DPPF-ligated palladium were markedly faster than the azole arylations. The combination of $Pd(OAc)_2$ and DPPF catalyzed the arylation of benzophenone imine, which contains an sp^2-hybridized nitrogen with a more basic electron pair, at 65−95 °C over the course of several hours. The imine arylation with DPPF-ligated palladium is general for electron-poor, electron-rich, and sterically hindered aryl halides. For reactions of aryl halides with electron-donating substituents, NaO-*t*-Bu was a superior base to Cs_2CO_3. Reactions of these substrates with Cs_2CO_3 as base produced substantial amounts of products resulting from exchange of the aryl halide with the phosphine aryl groups, and they were not pursued in detail.

The important fundamental question raised by this catalytic chemistry concerns the rates for reductive elimination of potential azolyl and methyleneamido intermediates, since the rates of the catalytic reaction may or may not reflect the rates for the actual C−N bond-forming step. Thus, we prepared palladium azolyl and methyleneamido aryl complexes with both DPPF and PPh_3 ligands, as shown in Scheme 1. Reaction of DPPF- or PPh_3-ligated aryl halide complexes **1** or **2** with excess potassium or sodium pyrrolyl formed anionic complexes **3** and **4** by displacement of one of the palladium−phosphine linkages. Neutral bisphosphine complexes **5** and **6** were prepared by addition of 1.05 equiv of potassium pyrrolyl. Palladium aryl methyleneamido complexes could not be isolated because they were more reactive toward reductive elimination, but they were generated in high yield and characterized in solution by ^1H and ^{31}P NMR spectrometry, as well as by IR spectroscopy. Reaction of $KN{=}CPh_2$ with $(DPPF)Pd(C_6H_4\text{-}t\text{-}Bu)(Br)$ formed $(DPPF)Pd(C_6H_4\text{-}t\text{-}Bu)(N{=}CPh_2)$ (**7**) after minutes at room temperature. Alternatively, this complex was generated at −10 °C by reaction of $HN{=}CPh_2$ with $(DPPF)Pd(C_6H_4\text{-}t\text{-}Bu)(O\text{-}t\text{-}Bu)$.[13,14]

The importance of using a chelating phosphine and a base that generates only small amounts of pyrrolyl anion was shown by the reaction chemistry in Scheme 1. The anionic PPh_3 complex **3** reacted at 120 °C to give a mixture of phosphine-ligated Pd(0) complexes, but *N*-aryl pyrrole was formed in only 11% yield. The neutral PPh_3 complex **5** also formed Pd(0) at 120 °C but produced *N*-aryl azole in a modest yield of 20%. These results contrasted the high-yielding reductive eliminations of arylamines under mild conditions from analogous PPh_3-ligated amido aryl complexes and showed that the coupling reaction to form a C−N bond between an aryl and a nitrogen-bound heteroaromatic ligand is less favorable than the formation of a C−N bond between an aryl group and an amide.[5] Furthermore, C−N reductive elimination of *N*-aryl azoles is much less favorable than C−C reductive elimination of biaryls.

DPPF-ligated palladium pyrrolyl aryl complexes reductively eliminated *N*-aryl pyrrole in higher yields than the PPh_3 analogues. The anionic DPPF complex **4** underwent reductive elimination in 15 h at 120 °C, but again in a modest 40% yield. However, the neutral DPPF complex **6** underwent reductive elimination of *N*-aryl pyrrole in the presence of PPh_3 in 89% yield at 100 °C over the course of 15 h. This result demonstrated that palladium azolyl complexes with the proper ligand set do undergo C−N bond-forming reductive elimination in high yields. Further, the comparison in yields and rates for reaction of anionic **4** and neutral **6** showed the importance of preventing formation of anionic pyrrolyl complexes to observe high yields in catalytic reactions. Indeed, the reaction of 4-bromo-*tert*-butylbenzene with sodium pyrrolyl catalyzed by DPPF−palladium occurred in 29% yield, significantly lower than the reactions of aryl bromide with pyrrole and alkoxide or carbonate base.

Methyleneamido complex **7** underwent reductive elimination of *N*-aryl imine in quantitative yield in less than an hour at room temperature. This observation confirmed our solution structural assignment of **7** and demonstrated a large difference in reductive elimination rates for complexes with different types of sp^2-hybridized nitrogens bound to palladium, one aromatic and one unsaturated. The rate for reductive elimination of the *N*-aryl imine is more similar to the rates of C−N bond-forming reductive elimination of arylamines or C−C bond-forming reductive elimination of styrenes than it is to the C−N(sp^2) bond-forming reductive elimination of *N*-aryl azoles.

At the outset of this study, it was unclear whether the reductive eliminations of *N*-aryl azoles and imines would be rapid in analogy to biaryl and styrene formation, or whether these reactions would be slow because arylamine reductive elimination rates decrease with decreasing amide group nucleophilicity.[3d,5] Our data show that reductive eliminations that form *N*-aryl azoles require higher temperatures than do reductive eliminations that form the C−C bonds in biaryls or the C−N bond in anilines, while elimination of *N*-aryl imines occurs at rates comparable to those of C−C reductive elimination. These data raise the possibility that the nucleophilicity of the nitrogen electron pair is an important factor in dictating reaction rates[15] because the nitrogen electron pair in azoles is involved in the heterocyclic aromatic system. Detailed kinetic studies that probe the mechanism and electronics of the different reductive elimination reactions and synthetic applications of these new C−N coupling processes will be the subject of future studies.

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Supporting Information Available: General procedures, ^1H,^{13}C NMR and mass spectra of all products in Table 1, literature references to previously reported products, and experimental procedures and spectral data for new compounds (55 pages). See any current masthead page for ordering and Internet access instructions.

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(12) $Pd(dba)_2$ (dba = bis(dibenzylidene)acetone) was an equally effective catalyst precursor in these reactions, but it was difficult to purify the reaction products from the dba that remained in the final reaction solution. $Pd(dba)_2$ was synthesized according to: Takahashi, Y.; Ito, Ts.; Sakai, S.; Ishii, Y. *J. Chem. Soc., Chem. Commun.* **1970**, 1065−6.

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(14) Characteristic spectroscopic features of **7** included two new doublet resonances in the ^{31}P NMR spectrum, four new cyclopentadienyl resonances (δ 3.82, 3.93, 4.28, 4.44) and one *tert*-butyl resonance (δ 1.12 ppm) in the ^1H NMR spectrum, and a $\nu_{C=N}$ band at 1604 cm^{-1} in the IR spectrum.

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