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Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery that Xantphos Can Be Trans-Chelating in a Palladium Complex

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Abstract: A general method for the intermolecular coupling of aryl halides and amides using a Xantphos/Pd catalyst is described. This system displays good functional group compatibility, and the desired C−N bond forming process proceeds in good to excellent yields with 1−4 mol % of the Pd catalyst. Additionally, the arylation of sulfonamides, oxazolidinones, and ureas is reported. The efficiency of these transformations was found to be highly dependent on reaction concentrations and catalyst loadings. A Pd complex resulting from oxidative addition of 4-bromobenzonitrile, (Xantphos)Pd(4-cyanophenyl)(Br) (**II**), was prepared in one step from Xantphos, $Pd_2(dba)_3$, and the aryl bromide. Complex **II** proved to be an active catalyst for the coupling between 4-bromobenzonitrile and benzamide. X-ray crystallographic analysis of **II** revealed a rare trans-chelating bisphosphine-Pd(II) structure with a large bite angle of 150.7°.

Introduction

Palladium-catalyzed C−N bond-forming reactions between aryl halides and amines have been extensively studied in the past few years.[1] These amination reactions can be carried out under mild conditions. Such processes enjoy excellent functional group tolerance and wide substrate scope. The analogous Pd-catalyzed C−N cross-coupling reactions with amides or sulfonamides, however, have been less generally successful.[2−11] Although it has been well-known that aryl halides react with various amides under Ullmann-type conditions (the Goldberg reaction), stoichiometric amounts of copper salts, high temperatures (>150 °C), and polar solvents such as DMF, collidine, and pyridine are usually required.[2,3] The substrate scope of these copper-mediated amidations has traditionally been quite limited as well. Recently, we described an improved copper-based system that is able to effect the coupling of aryl iodides and amides, as well as several nitrogen heterocycles, using 0.2−10 mol % of CuI.[4]

One of our initial forays into Pd-catalyzed C−N bond-forming reactions included the investigation of intramolecular couplings of aryl bromides and amides to form five- to seven-membered rings,[5a] and subsequent work in our group has allowed for the extension of this chemistry to carbamate and sulfonamide substrates.[5b] These transformations can be accomplished with P(*o*-Tol)$_3$, P(2-furyl)$_3$, BINAP, or other chelating phosphines as the ligand and K_2CO_3 or Cs_2CO_3 as the base.[5]

Other groups have reported Pd-catalyzed C−N bond-forming reactions involving amides and related nitrogen nucleophiles. For example, Shakespeare found that intermolecular reactions between lactams and aryl bromides could be effected with a DPPF-based catalyst system.[6] Skerjl described the arylation of *tert*-butylcarbazate with a DPPF/Pd(OAc)$_2$ catalyst,[7] and Arterburn recently extended this method to the reaction of halopyridines.[8] In a related process, Hartwig has reported that aryl bromides and chlorides can be effectively coupled with *tert*-butyl carbamate by using P(*t*-Bu)$_3$ as ligand and sodium phenoxide as base.[9] Using an electron-rich, hindered biaryl-based phosphine, Edmondson effected the intermolecular coupling between aryl halides and vinylogous amides.[10] Additionally, Bolm and Harmata have reported the Pd-catalyzed *N*-arylation of sulfoximines,[11] while Beletskaya and co-workers have recently described the use of ureas as substrates in Pd-catalyzed C−N bond-forming processes.[12] Last year, we reported a reasonably general Pd-based catalyst for the inter-

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(1) (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174 and references therein.
(2) For a review on Cu-catalyzed cross-coupling reactions, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1435−1456.
(3) Examples of CuI-mediated *intramolecular* amidations under relatively mild conditions have been reported: Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277−280.
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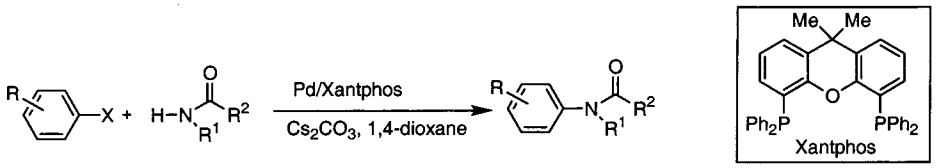
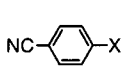
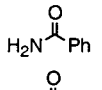
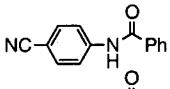
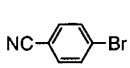
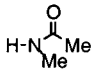
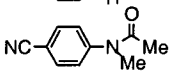
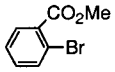
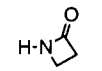
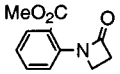
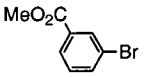
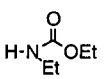
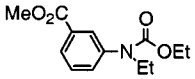
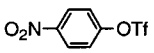
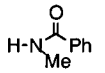
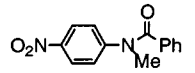
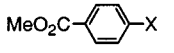
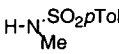
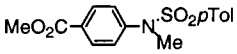
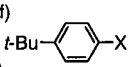
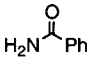
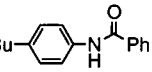
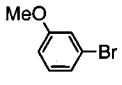
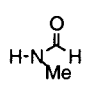
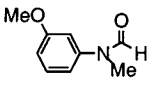
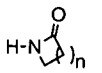
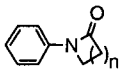
(9) Hartwig, J. F.; Kawatsura, M.; Hauck, S. L.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.
(10) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109−1112.
(11) (a) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731−5734. (b) Harmata, M.; Pavri, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2419−2421. (c) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, 911−913. (d) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169−175.

Table 1. Pd-Catalyzed Amidation of Activated and Unactivated Aryl Halides[a]



Entry	ArX	Amide	Product	mol% Pd	T (°C)	t (h)	Yield (%)
1 (X=Br)				1	45	19	93[a,b]
2 (X=I)				1	45	18	98[a,b]
3				1	45	42	97[a,b]
4				1	100	35	78[a,d]
5				2	110	44	66[a,d]
6				1	80	16	74[a]
7				2	100	22	87[a]
8 (X=OTf)				4	100	16	94[d,e]
9 (X=I)				2.5	100	16	89[d,e]
10 (X=Br)				2.5	100	16	91[d,e]
11				1	100	16	99[a]
12 (n=1)				1	100	16	93[d]
13 (n=2)				1	100	16	96[d]
14 (n=3)				1	100	32	92[d]
15 (n=4)				1	100	22	90[d]

[a] Reaction conditions: 1.0 equiv of aryl halide/triflate, 1.1−1.2 equiv of amide/carbamate/sulfonamide, Xantphos/$Pd(OAc)_2$ = 1.5/1, 1.4−1.5 equiv of Cs_2CO_3, 1,4-dioxane ([halide/triflate] = 1 M). Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^1H NMR and GC analysis or combustion analysis. [b] THF as solvent. [c] 1.2 equiv of aryl bromide and 1.0 equiv of sulfonamide were used. [d] Reaction conditions: 1.0 equiv of the aryl halide/triflate, 1.2 equiv of amide, Xantphos/$Pd_2(dba)_3$ = 3/1 (L/Pd = 1.5/1), 1 mol % Pd refers to 0.5 mol % $Pd_2(dba)_3$, 1.4 equiv of Cs_2CO_3, 1,4-dioxane ([halide/triflate] = 1 M); 100 °C. [e] [halide/triflate] = 2 M.

molecular coupling of aryl halides and amides.[13] In this paper, we disclose in full the results of this investigation as well as the discovery of a surprising trans-chelating bis(phosphine) Pd(II) complex that was demonstrated to be a competent catalyst in the amide arylation reaction.

Results and Disussion

To establish the viability of the amide coupling process, we undertook an intensive screening of a variety of ligands and reaction variables. We found that a Pd catalyst using Xantphos, a ligand developed by van Leeuwen,[14] with Cs_2CO_3 as the base and THF or 1,4-dioxane as the solvent provided the most generally successful catalyst for the coupling of amides with activated (electron deficient) as well as electronically neutral aryl halides.

During the study of various reaction variables, we found that $Pd(OAc)_2$ was the Pd source of choice in reactions involving electron-deficient aryl halides. Representative results are summarized in Table 1 (entries 1−7). Activated aryl bromides, iodides, and triflates could be cleanly coupled. Electron-withdrawing groups such as nitriles (entries 1−3), esters (entries 4, 5, and 7), and nitro groups (entry 7) were well tolerated.

For electronically neutral and electron-rich aryl halides, the desired C−N bond formation was less straightforward. For example, under the conditions used for the successful reaction between 4-bromobenzonitrile and benzamide, the coupling between 4-*tert*-butylbromobenzene and benzamide afforded none of the desired product. Subsequent screening of reaction conditions revealed that by using $Pd_2(dba)_3$ as the palladium

(12) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381−4384.
(13) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104.
(14) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081−3089. Previous uses of Xantphos in C−N bond-forming reactions: (b) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789−3790. (c) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (d) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019−6022. For a kinetic study of Xantphos/Pd-catalyzed amine arylation reactions, see: (e) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475−482.

source and Xantphos as the ligand, the amidation of unactivated aryl halides could be efficiently carried out (entries 8−15). Electronically neutral or slightly electron-rich aryl halides or triflates reacted efficiently with both aromatic and aliphatic primary amides, *N*-methylformamide (entries 12), and lactams (entries 12−15) at 100 °C. It is worth mentioning that couplings between bromobenzene and four- to seven-membered-ring lactams could generally be realized with as little as 1 mol % of Pd at 100 °C. Notably, under these basic conditions, none of the product resulting from ring opening was observed.

When less reactive aryl halides were used, small amounts (2−8%) of *N*-phenylated amides were detected as the byproducts in crude reaction mixtures (GC and GC-MS analysis); removal of these side products was straightforward with flash chromatography. Increasing the Xantphos:Pd ratio usually resulted in increased amounts of the *N*-phenylamide. These byproducts are likely formed via exchange between the aryl group bound to Pd(II) and the phenyl group of the phosphine ligand;[15] Hartwig and co-workers have observed similar aryl group exchange processes in Pd-catalyzed aminations.[15a]

During the course of these studies, we found an unusual dependence of catalyst loading on the reaction efficiency. For example, using 5 mol % of Pd (as Pd_2dba_3)/7.5 mol % of Xantphos in the coupling of 4-*tert*-butylbromobenzene and benzamide, a product:ArBr ratio of 1:5 was obtained as compared to 1.1:1 with 2 mol % of Pd, implicating the possibility of an unknown catalyst decomposition pathway occurring at higher catalyst concentrations. Notably, higher amounts of *N*-phenylated side products were observed at higher catalyst loadings as well (∼1 M in ArBr).

At this point in our investigations, the amidations of activated aryl halides were fairly general, but the scope of the amidation involving unactivated aryl halides was still limited. For example, acyclic secondary amides as well as sulfonamides were unreactive, and sterically hindered or electron-rich unactivated aryl halides were not viable substrates under the optimized conditions shown above. Additionally, aryl group exchange became more problematic in these challenging couplings, and increasing amounts of the phenylated byproduct was observed. Generally, higher catalyst loadings may be used to accelerate a reaction; however, for these amidation processes, additional catalyst often led to an increase in aryl group exchange product and faster decomposition of the catalyst. Unfortunately, replacement of the phenyl groups on Xantphos with *o*-tolyl groups to suppress aryl group exchange yielded an inefficient amidation catalyst. A detailed examination of the reaction parameters led to the discovery that careful control of catalyst loading *and* the reaction concentration was key to the successful amidation of less reactive substrates.

A substrate concentration of 1 M was suitable for most cases reported in Table 1; however, lower concentrations (0.125 to 0.5 M) and higher palladium catalyst loadings were required for these more challenging reactions to proceed efficiently. Lower concentrations may decrease the rate of catalyst decomposition, particularly when more catalyst was used.

With a better understanding of the reaction variables important to the success of these couplings, we sought to extend the methodology to more challenging substrate combinations (Table 2). Thus, with 4 mol % of Pd and a concentration of 0.5 M, 2-bromotoluene reacted with benzamide in 98% yield (entry 1). The lactam 2-pyrrolidinone was also coupled with sterically hindered 2-bromo-*p*-xylene at 0.25 M (88% yield, entry 2). Electron-rich aryl halides such as 2-bromoanisole and 2-iodoanisole both underwent amidations in good yields (entries 3 and 4). Previously extremely inactive amides such as *N*-methylacetamide (an acyclic secondary amide), as well as a primary or secondary sulfonamide, also reacted with unactivated aryl bromides under these more controlled conditions (entries 5−7). It is interesting to note that although dioxane has been the solvent of choice for most amidations, toluene proved to be the preferred solvent for the coupling of the secondary sulfonamide *N*-methyl *p*-tolylsulfonamide (entry 6).

We also examined the C−N bond-forming reactions using other amide analogues such as cyclic carbamates[7−9] and ureas.[12] With K_3PO_4 as base, 2-oxazolidone reacted with 4-chlorobromobenzene in 87% yield (entry 8). Both five- and six-membered cyclic ureas were doubly arylated with 3-bromoanisole with as little as 1 mol % of the palladium catalyst (entries 9 and 10). In the latter two cases, increasing the loading of the palladium catalyst and Xantphos ligand resulted in an increase of the aryl group exchange byproducts.

The Pd-catalyzed amidations of aryl halides described above have shown very good substrate scope and functional group compatibility. Aryl halides bearing electron-withdrawing groups at ortho, meta, or para positions underwent C−N bond formation reactions generally with primary and secondary amides, carbamate, and sulfonamides. Unactivated or deactivated aryl halides also coupled with various amides under more carefully controlled conditions. However, a few classes of substrate combinations still remain challenging for this Pd−catalyst system. Amidations of aryl halides bearing a ketone functional group suffered from a competitive ketone arylation processes. Additionally, amidation reactions involving aryl halides that possess a para-electron-donating group or acyclic secondary amides were usually sluggish and yielded large amounts (>20%) of aryl group exchange products (*N*-phenyl amides).

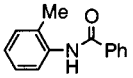
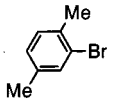
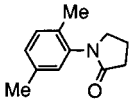
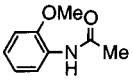
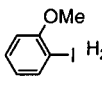
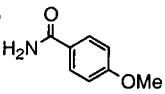
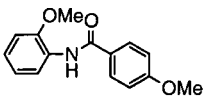
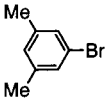
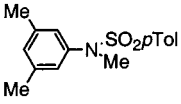
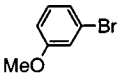
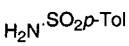
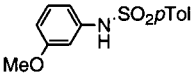
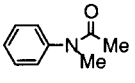
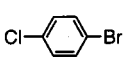
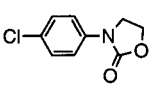
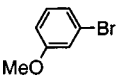
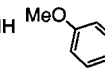
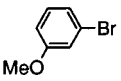
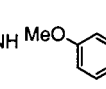
The fact that only Xantphos worked efficiently for amidation reactions prompted us to study the mechanism of the reaction in greater detail. To this end, we first tried to isolate the oxidative addition product from 4-bromobenzonitrile, $Pd_2(dba)_3$, and Xantphos. (Bisphoshine)Pd(Ar)X complexes have been prepared from their monophosphine complex dimers $[(P(o\text{-}Tol)_3)Pd(Ar)X]_2$[16] (**I**) or $[(PPh_3)Pd(Ar)X]_2$.[17] Following a procedure used to prepare (BINAP)Pd(4-cyanophenyl)(Br) in our laboratories,[16] complex **I** underwent ligand exchange when treated with Xantphos in methylene chloride at room temperature to afford the corresponding Xantphos complex, (Xantphos)Pd(4-cyanophenyl)(Br) (**II**), which is air-stable and can be stored in a vial on the bench for over a year without noticeable decomposition, as judged by NMR (Scheme 1). We subsequently found that complex **II** could be prepared in 80% yield by simply stirring 4-bromobenzonitrile, $Pd_2(dba)_3$, and Xantphos in benzene at room temperature for 22 h. To our surprise, complex **II** showed only one singlet in ^{31}P NMR at +9.3 ppm, compared to a pair

(15) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694−3703. For a mechanistic study, see: (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am.Chem. Soc.* **1997**, *119*, 12441−12453.

(16) (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787−6795. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504−6511.

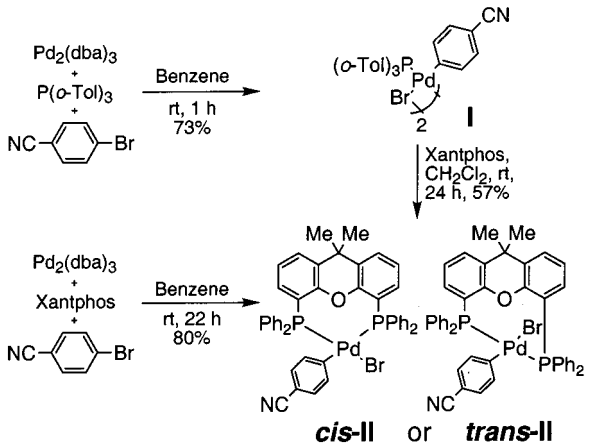
(17) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232−8245.

Table 2. Pd-Catalyzed Amidation of Less Reactive Substrates[a]

Entry	Halide	Amide	Product	mol% Pd	conc (M)	t (h)	Yield (%)
1				4	0.5	15	98
2				4	0.25	15	88
3				2	0.5	15	97
4				4	0.25	46	72[b]
5				1	0.125	38	82[c,d]
6				4	0.25	47	56[e]
7				4	0.25	37	73
8				2	0.125	16	87[f]
9				1	0.25	44	92[g]
10				1	0.5	44	97[g]

[a] Reaction conditions: 1.0 equiv of the aryl halide/triflate, 1.2 equiv of amide, Xantphos/$Pd_2(dba)_3$ = 3/1 (L/Pd = 1.5/1), 1 mol % of Pd refers to 0.5 mol % of $Pd_2(dba)_3$, 1.4 equiv of Cs_2CO_3, 1,4-dioxane, 100 °C. Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^1H NMR, and GC analysis or combustion analysis. [b] 95% conversion. [c] Run in toluene at 120 °C. [d] 0.5 mmol of sulfonamide and 0.6 mmol of bromide were used. [e] Run at 120 °C. [f] K_3PO_4 as base. [g] 0.5 mmol of urea, 1.4 mmol of bromide, and 1.4 mmol of Cs_2CO_3 were used.

Scheme 1



of doublets (J = 38.4 Hz) at +27.9 and +12.9 ppm of the (BINAP)Pd(4-cyanophenyl)(Br), which has a normal cis-chelating structure. The corresponding iodide complex, (Xantphos)-Pd(4-cyanophenyl)I, was prepared in a similar fashion and also displayed one singlet at +9.9 ppm by ^{31}P NMR. These data suggested the possibility of a trans-chelating structure (*trans*-**II**). Van Leeuwen has previously reported a cis-chelating Xantphos-Pd(0) tetracyanoethylene complex as well as a *cis*-Xantphos-Pd(II) allyl complex,[18,19] and after the completion of our work, he very recently has reported a trans-chelated Xantphos-Pd(Me)Cl complex, which was characterized crystallographically.[20]

The unambiguous assignment of the structure of complex **II** was possible through X-ray crystallography. As shown in Figure 1, the complex features a rare trans-chelating structure.[20,21] The aryl group (4-cyanophenyl) and the bromide are trans to each

(18) Kranenburg, M.; Delis, J. G. P.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vrieze, K.; Veldman, N.; Spek, A. L.; Goubitz, K.; Fraanje, J. *J. Chem. Soc., Dalton Trans.* **1997**, 1839−1849.
(19) van Haaren, R. J.; Goubitz, K.; Fraanje, F.; van Strijdonck, G. P. F.; Oevering, H.; Coussens, B.; Reek, J. N. H.; van Leeuwen, P. W. N. M. *Inorg. Chem.* **2001**, *40*, 3363−3372.
(20) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895−904.
(21) *trans*-Pd complexes have been observed with Transphos and long-chain bisphosphines: (a) Bachechi, F.; Zambonelli, L.; Venanzi, L. M. *Helv. Chim. Acta* **1977**, *60*, 2815−2823. (b) March, F. C.; Mason, R.; Thomas, K. M.; Shaw, B. L. *Chem. Commun.* **1975**, 584. (c) Alcock, N. W.; Brown, J. M.; Jeffery, J. C. *Chem. Commun.* **1974**, 829.

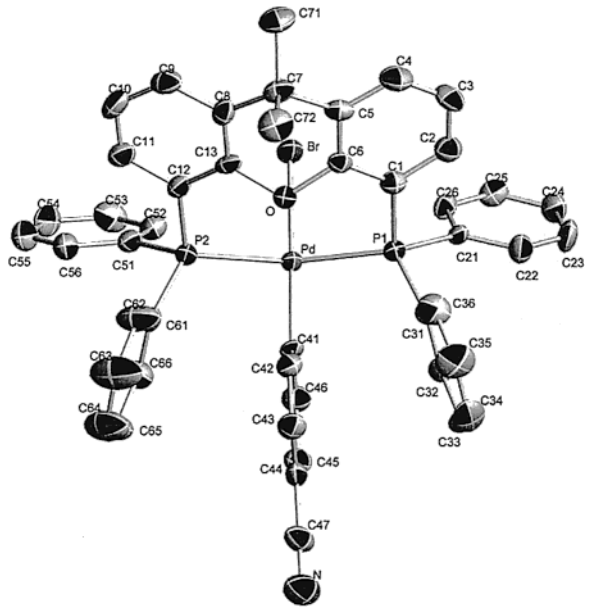


Figure 1. ORTEP structure of **II**.

other, with a C−Pd−Br angle of 176.4° in the distorted square-planar Pd complex. The two phosphorus atoms are trans to each other with a bite angle[22] (P−Pd−P) of 150.7°, much larger than 104.6° observed by van Leeuwen in the *cis*-(Xantphos)Pd-(TCNE) complex and closer to the 153° bite angle measured in the *trans*-(Xantphos)Pd(Me)Cl crystal structure.[23] Notably, the observed angle is also beyond the calculated flexible bite angle range of Xantphos (97−135°) and much larger than the bite angles (72−131°) of most commonly used bidentate phosphine ligands. This unusually large bite angle might be a result of the weak interaction of the oxygen atom with the Pd (Pd−O distance = 2.697 Å).[23,24] Although the Pd−P bond lengths of complex **II** (2.304 and 2.311 Å) are even slightly shorter than those seen in the (Xantphos)Pd(TCNE) (**A**) (2.356 and2.352 Å), the P1−P2 bond length of complex **II** is much longer (4.466 Å compared to 3.726 Å of **A** and 4.080 Å of free Xantphos[25]) due to the large bite angle.

Complex **II** proved to be a competent precatalyst for the amidation of 4-bromobenzonitrile with benzamide that was comparable to the in situ generated $Pd_2(dba)_3$/Xantphos complex. With 1 mol % of complex **II**, the reaction between 4-bromobenzonitrile and benzamide went to completion in 23 h at 45 °C to provide the desired product in 96% yield. The trans-chelating structure of complex **II** raises the question of how the reductive elimination occurs from such a *trans*-Pd complex.[26] Presumably, dissociation of one of the coordinating phosphine groups with reductive elimination from a three-coordinate intermediate[27] or isomerization to the cis isomer followed by reductive elimination takes place.[26b] Unfortunately, attempts to prepare the analogous Pd(II) amide complex, the proposed intermediate formed prior to reductive elimination, have been unsuccessful.

Conclusions

The first general intermolecular cross-coupling between aryl halides or triflates and amides, sulfonamides, and carbamates has been developed by using a Xantphos/Pd catalyst, Cs_2CO_3 as the base, and dioxane (or THF) as the solvent. This amidation protocol enjoys a reasonably broad substrate scope and good functional group compatibility. Activated aryl halides that bear electron-withdrawing groups at ortho, meta, or para positions efficiently underwent C−N bond formation with primary and secondary amides, as well as carbamates and sulfonamides. Unactivated or deactivated aryl halides also reacted with various amides under more carefully controlled conditions to prevent unwanted side reactions such as aryl exchange with the phosphine or catalyst deactivation. During our studies, we prepared a rare trans-chelating palladium(II) complex, (Xantphos)-Pd(4-cyanophenyl)(Br) (**II**), which was readily prepared from Xantphos, $Pd_2(dba)_3$, and 4-bromobenzonitrile. Complex **II** proved to be an effective catalyst for the coupling of 4-bromobenzonitrile and benzamide whose activity was comparable to the catalyst generated in situ from $Pd_2(dba)_3$ and the ligand.

Experimental Section

General Procedure for Pd-Catalyzed Couplings of Aryl Halides or Triflates and Amides, Carbamates, or Sulfonamides (Tables 1 and 2). The reactions in Table 1 were performed on a 1.0 mmol scale unless mentioned otherwise, and those in Table 2 were all performed on a 0.5 mmol scale. A flame-dried resealable Schlenk tube was charged with $Pd(OAc)_2$ or $Pd_2(dba)_3$ (NOTE: 0.5 mol % $Pd_2(dba)_3$ refers to 1 mol % of Pd) as indicated in the tables, Xantphos (L/Pd = 1.5), the solid reactant(s) (1.0 equiv of the aryl halide/triflate and 1.2 equiv of the amide, carbamate, or sulfonamide), and Cs_2CO_3 (1.4 equiv). The Schlenk tube was capped with a rubber septum, evacuated, and backfilled with argon twice. The liquid reactant(s) and anhydrous 1,4-dioxane (1 mL/mmol aryl halide or triflate or according to the concentration indicated in the table) were then added by syringe through the septum. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at the indicated temperature (45−120 °C) for the times indicated in the table (6 − 46 h) until the starting aryl halide or triflate had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with dichloromethane (10 mL), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

Synthesis of the Oxidative Addition Pd Complex II. A solution of Xantphos (128 mg, 0.22 mmol, 1.1 equiv), $Pd_2(dba)_3$ (92 mg, 0.10 mmol, 0.20 mmol Pd, 1.0 equiv), and 4-bromobenzonitrile (168 mg, 0.92 mmol, 4.6 equiv) in benzene (6 mL) was stirred at room temperature for 22 h. The mixture was then filtered through a pad of Celite and concentrated in vacuo. Ether (6 mL) was then added to the residue and yellow crystalline solid was allowed to form upon standing for 1 h. The solid was then filtered, washed with ether, and dried under vacuum to give 140 mg (80%) of complex **II**: mp >195 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 6.8, 2.4 Hz, 2 H), 7.29−

(22) (a) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519−1529. For an excellent review on ligand bite angle effects, see: (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769.

(23) A weak interaction of a third atom with Pd could lead to large bite angles. See (a) ref 18. Complex $[(DPPF)Pd(PPh_3)](BF_4)_2$ also shows a big bite angle of 155.9° with an Fe−Pd bond: (b) Sato, M.; Shigeta, H.; Sekino, M. *J. Organomet. Chem.* **1993**, *458*, 199−204.

(24) Pd−O distances observed in a few Pd complexes range from 2.02 to 2.14 Å. See: (a) Alsters, P. L.; Boersma, J.; Smeets, W. J. J.; Spek, A. V.; van Koten, G. *Organometallics* **1993**, *12*, 1639−1647. (b) Alsters, P. L.; Baesjou, P. J.; Janssen, M. D.; Kooijman, H.; Sicherer-Roertman, A.; Spek, A. V.; van Koten, G. *Organometallics* **1992**, *11*, 4124−4135.

(25) The distance was reported to be 4.045 Å by Haenel. See: Hillebrand, S.; Bruckmann, J.; Krüger, C.; Haenel, M. W. *Tetrahedron Lett.* **1995**, *36*, 75−78.

(26) For discussions of reductive elimination from Pd, see: (a) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933−4941 (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860.

(27) This is consistent with our work involving bulky, electron-rich ligands which are believed to yield L−Pd complexes after their reaction.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for Complex **II**

Pd−P(1)	2.3114(16)	Pd−P(2)	2.3042(16)
Pd−Br	2.5324(19)	Pd−C(41)	1.996(5)
C(41)−Pd−P(2)	90.35(16)	C(41)−Pd−P(1)	89.64(16)
P(2)−Pd−P(1)	150.70(6)	C(41)−Pd−Br	176.44(17)
P(2)−Pd−Br	89.62(4)	P(1)−Pd−Br	92.12(4)
C(1)−P(1)−Pd	104.11(19)	C(12)−P(2)−Pd	104.78(19)

6.75 (m, 36 H), 6.33 (br s, 2 H), 1.81 (br s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 155.5, 155.4, 155.3, 134.92, 134.89, 134.86, 131.88, 131.1, 130.81, 130.5, 130.1, 128.5, 128.1, 127.5, 124.62, 124.58, 121.7, 121.4, 121.1, 120.5, 103.8, 36.42, 36.40, 36.37 (observed complexity due to P−C splitting); ^{31}P NMR (121 MHz, C_6D_6) δ +9.3; IR (neat, cm^{-1}) 3053, 2971, 2218, 1571, 1434, 1399, 1211, 745, 695. Anal. Calcd for $C_{46}H_{36}BrNOP_2Pd$: C, 63.85; H, 4.18. Found: C, 63.67; H, 4.12.

Amidation with Complex II as the Catalyst. A flame-dried Schlenk tube was charged with complex **II** (4.3 mg, 0.005 mmol, 1%), 4-bromobenzonitrile (91 mg, 0.50 mmol, 1.0 equiv), benzamide (67 mg, 0.55 mmol, 1.1 equiv), and Cs_2CO_3 (245 mg, 1.5 mmol, 1.5 equiv), evacuated, and backfilled with argon. THF (0.5 mL) was then added through syringe. The Schlenk tube was sealed and heated at 45 °C for 23 h when GC analysis revealed complete conversion of the aryl bromide. The mixture was then diluted with methylene chloride (10 mL), filtered, concentrated, and purified by flash column chromatography (silica gel) to give 108 mg (97%) (second run gave 105 mg, 95%) of *N*-(4-cyanophenyl)benzamide as a white solid.

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Supporting Information Available: Characterization data for all new products and details of the X-ray structure of complex **II** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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