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Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational, and Synthetic Investigation

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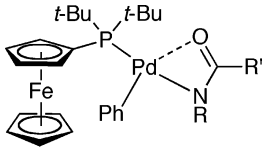
Abstract: We present results on the amidation of aryl halides and sulfonates utilizing a monodentate biaryl phosphine-Pd catalyst. Our results are in accord with a previous report that suggests that the formation of κ^2-amidate complexes is deleterious to the effectiveness of a catalyst for this transformation and that their formation can be prevented by the use of appropriate bidentate ligands. We now provide data that suggest that the use of certain monodentate ligands can also prevent the formation of the κ^2-amidate complexes and thereby generate more stable catalysts for the amination of aryl chlorides. Furthermore, computational studies shed light on the importance of the key feature(s) of the biaryl phosphines (a methyl group *ortho* to the phosphorus center) that enable the coupling to occur. The use of ligands that possess a methyl group *ortho* to the phosphorus center allows a variety of aryl and heteroaryl chlorides with various amides to be coupled in high yield.

Introduction

The copper-[1] and palladium-catalyzed[2] amidation of aryl bromides and iodides have become well-established processes in organic synthesis. However, largely absent from the literature on Pd-catalyzed amidation reactions is the description of an efficient and general method for coupling aryl chlorides.[3] It is unlikely that this is due to the inability of phosphine-Pd catalysts to oxidatively add to aryl chlorides, as numerous ligands, in the past 10 years, have been shown to promote oxidative addition to even extremely hindered aryl chlorides.[4] More likely, a ligand has yet to be developed that is capable of promoting oxidative addition to aryl chlorides *and* reductive elimination of an amidate ligand from Pd(II) centers, while supporting a reasonable rate of "transmetallation" to form the amidate intermediate. Further complicating matters is that, in the catalytic cycle for palladium-catalyzed amidation reactions, it is likely that the formation of κ^2-amidate complex,[5] e.g., complex **1**, where the amidate is bound to the palladium center at both the oxygen and nitrogen atoms, inhibits reductive elimination and therefore catalytic turnover. Recently, a study concerning Pd-catalyzed amidation suggested that reductive elimination to form the C−N bond of N-aryl amides can occur more readily from complexes generated from bidentate phosphine ligands than from monodentate phosphine ligands as a result of the inhibition of the formation of a κ^2-amidate complex.[6] Since reports from our laboratory,[2c] as well as others,[2d,3c] on the Pd-catalyzed amidation of aryl halides and sulfonates have demonstrated monodentate biaryldialkyl phosphines as components of highly active catalyst systems, we felt that it was important to investigate the origin of the enhanced activity that is observed with these particular monodentate ligands.



κ^2-Amidate (**1**)

Herein we present the first general catalytic system capable of the facile amidation of aryl chlorides by utilizing a finely

(1) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655. (d) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533. (e) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120−4121.

(2) (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043−6048. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655. (d) Willis, M. C.; Brace, G. M.; Holmes, I. P. *Synthesis* **2005**, 3229−3234. (e) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185−1188.

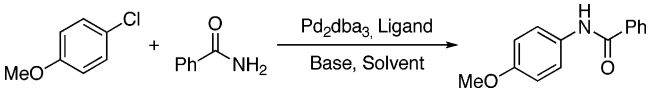
(3) Pd-catalyzed intermolecular amidation of aryl chlorides: (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (b) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351−1354. (c) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207−2210. (d) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433−2435. (e) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371−1375. (f) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411−1414. Examples of the intramolecular amidation of aryl chlorides: (g) Poondra, R. R.; Turner, N. J. *Org. Lett.* **2005**, *7*, 863−866. (h) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311−3314.

(4) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(5) For an example of a κ^2-bis(amidate) titanium complex, see: Zhang, Z.; Schafer, L. L. *Org. Lett.* **2003**, *5*, 4733−4736.

(6) Fujita, K.-i.; Yamashita, M.; Puschman, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044−9045.

Table 1. Optimization of Reaction Conditions for the Amidation of Aryl Chlorides



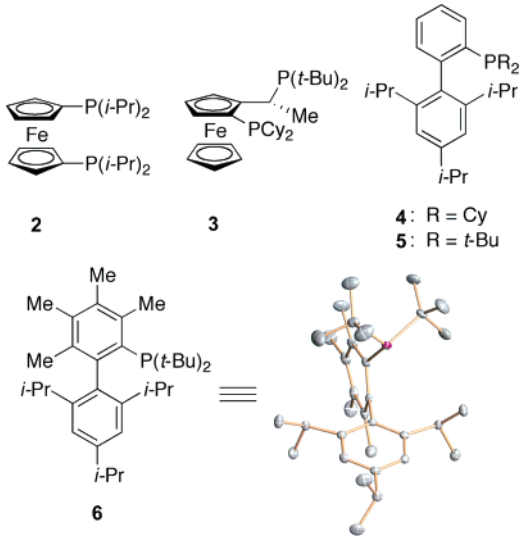
entry	ligand	base	solvent	conversion (%)[b]	yield (%)[c]
1	Xantphos[d]	Cs_2CO_3	*t*-BuOH	13	0[b]
2	**2**[e]	K_3PO_4	*t*-BuOH	0	0[b]
3	**3**[f]	K_3PO_4	*t*-BuOH	0	0[b]
4	**4**	K_3PO_4	*t*-BuOH	1	1[b]
5	**5**	K_3PO_4	*t*-BuOH	9	9[b]
6	**6**	K_3PO_4	*t*-BuOH	94	94
7	**6**	K_3PO_4	toluene	89	89
8	**6**	K_3PO_4	1,4-dioxane	79	79
9	**6**	K_2CO_3	*t*-BuOH	45	45[b]
10	**6**	Cs_2CO_3	*t*-BuOH	97	97
11	**6**	*t*-BuONa	*t*-BuOH	28	28[b]
12	**6**	LHMDS	toluene	1	1[b]

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amide, 1.2 equiv of base, solvent ([aryl chloride] = 0.5 M), 0.5 mol % Pd_2dba_3, 2.5 mol % ligand. [b]Determined by GC. [c]Isolated yields. [d]1.5 mol % Xantphos was used. [e]2 mol % **2**. [f]1 mol % **3**.

tuned monodentate phosphine ligand. These results confirm that monodentate phosphines can indeed be superior ligands for reactions of this type. Additionally, we provide a rationalization for the (in)efficacy of catalysts based on dialkylbiaryl phosphine ligands for the Pd-catalyzed amidation of aryl halides through the use of *all-atom* density functional theory (DFT). Finally, kinetic data suggest that transmetallation is the rate-limiting step in the amidation sequence.

Results

We initiated our investigation by examining the conditions under which the coupling reaction of 4-chloroanisole and benzamide proceeded efficiently (Table 1). Not unexpectedly, Xantphos [9,9-dimethyl-4-5-bis(diphenylphosphino)xanthene], which is a fairly general and efficient ligand for amidation reactions of aryl iodide and bromide substrates,[2a,2b] was inactive for the intermolecular amidation of chloroanisole (entry 1). Catalysts derived from ferrocene-based bisphosphine ligands such as 1,1′-bis(di-*i*-propylphosphino)ferrocene (**2**) and JosiPhos {(*R*)-(−)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine} (**3**) were also found to be ineffective (entries 2 and 3) *under all conditions studied*.[7] Although bulky biaryl monophosphine ligands **4** and **5** provided the desired coupling product, yields were <10% (entries 4 and 5). Based on other work from our laboratory, we postulated that increasing the bulk of the phosphine-containing aromatic ring may be necessary for mediating Pd-catalyzed amidation reactions of aryl chlorides. Indeed, the use of ligand **6**,[8] with four additional methyl groups on the upper ring of **5**, promoted the catalytic amidation of 4-chloroanisole with benzamide in 94% isolated yield (entry 6). We also determined that *t*-BuOH was the optimal solvent for this transformation presumably because amides and/or deprotonated amides are much more soluble in a protic solvent rather than in ethereal or hydocarbon solvents (entries 6−8).[1c] Finally, phosphate and carbonate bases were found to be more effective than stronger bases such as NaO*t*-Bu and LHMDS (entries 6 and 9−12).

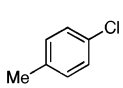
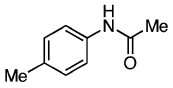


The scope of the palladium-catalyzed amidation of aryl chlorides was subsequently explored using Pd_2dba_3 as precatalyst, **6** as ligand, K_3PO_4 as base, and *t*-BuOH as solvent (Table 2). Both unactivated (entries 1−17) and activated (entries 18−20), as well as *ortho* substituted aryl chlorides (entries 11 and 12), were coupled with a variety of amides in good to excellent yields. A number of functional groups were tolerated under this set of reaction conditions. Of particular interest, aryl chlorides and amides containing a free hydroxy group (entries 13 and 14) and a secondary amine on the aromatic ring (entry 15) were converted to desired products in high yields. To the best our knowledge, these are the first examples of a palladium-catalyzed amidation reaction where phenols and secondary amine groups are compatible. A variety of primary amides, both aliphatic and aromatic, were also coupled in high yield. Molecular sieves (3 Å) were employed to suppress the formation of phenol derivatives[8a] for some activated aryl chlorides (entries 19 and 20). Notably, formamide (entries 4 and 9), sulfonamide (entry 5), and 2′,2′,2′-trifluoroacetamide (entries 6 and 18) can be coupled with aryl chlorides effectively under slightly modified reaction conditions. Formamide and trifluoromethylamide derivatives are particularly interesting as they can be used as precursors of free amine[9] and methylamine[10] compounds. Lactam (entry 3) and secondary formamide (entry 10) could also be coupled with aryl chlorides. However, the coupling of hindered secondary amides is problematic, most likely due to the reduced nucleophilicities of these amides relative to hydroxide under the reaction conditions (entry 21). Consequently, significant amounts of phenols and diaryl ethers are formed from aryl halides in these cases.[8a] It is important to note that although the coupling of amides with mono-*ortho* substi-

(7) We are not suggesting that these ligands cannot be the supporting ligand in successful coupling reactions of this type; however, their use did not lead to satisfactory results.

(8) (a) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694−10695. (b) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321−4326.
(9) (a) Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1555−1556. (b) Nakagawa, M.; Yokoyama, Y.; Kato, S.; Hino, T. *Tetrahedron* **1985**, *41*, 2125−2132. (c) Fleming, I.; Loreto, M. A.; Wallace, I. H. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349−359.
(10) (a) Brown, S. A.; Rizzo, C. J. *Synth. Commun.* **1996**, *26*, 4065−4080. (b) Minutolo, F.; Antonello, M.; Bertini, S.; Ortore, G.; Placanica, G.; Rapposelli, S.; Sheng, S.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A.; Macchia, M. *J. Med. Chem.* **2003**, *46*, 4032−4042.

Table 2. Coupling of Aryl Chlorides with Amides[a]

Entry	ArCl	Amide	Product	Pd (mol %)	Yield (%)[b]
1				1	99
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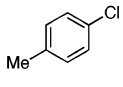
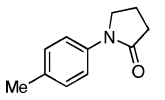
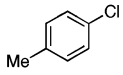
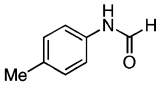
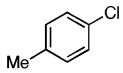
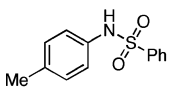
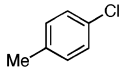
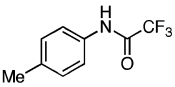
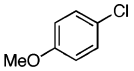
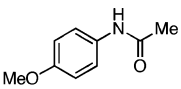
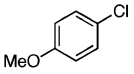
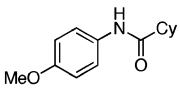
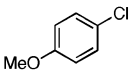
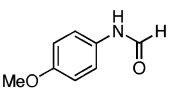
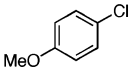
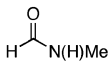
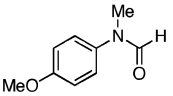
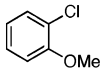
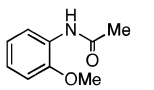
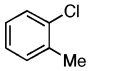
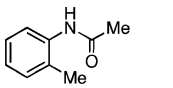
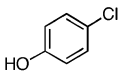
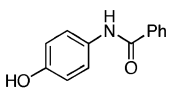
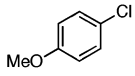
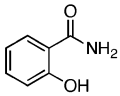
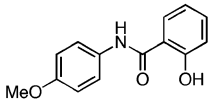
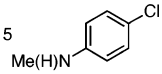
3				1	95
4				2	92[c,d]
5				2	87[c]
6				2	82[c,e]
7				1	99
8				1	96
9				4	82[c,d]
10				1	88
11				1	99
12				2	71
13				2	95
14				2	92
15				2	98
16				2	97
17				1	99
18				1	90
19				1	83[e]
20				1	85[e]
21				2	60[e]

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.0−1.5 equiv of amide, 1.2−1.5 equiv of K_3PO_4, *t*-BuOH ([aryl chloride] = 0.5 M), Pd_2dba_3 (0.125−2.0%), Ligand **6** (0.625−10.0%) (Pd/L = 1/2.5). [b]Yields represent isolated yields of compounds estimated to be ≥95% pure as judged by ^{1}H NMR, GC, and combustion analysis (average of two runs). [c]1.2−1.5 equiv of K_2CO_3 was used. [d]Ligand **5** was used (Pd/L = 1/2.5). [e]Molecular sieves (3 Å) were used.

tuted aryl chlorides can be performed (entries 11 and 12), reactions with substrates containing bulkier substituents (e.g., 2-chloroacetophenone) or with di-*ortho* substitution (e.g., 2-chloro-*m*-xylene) do not afford the desired product in any appreciable amount.

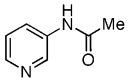
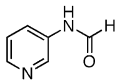
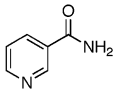
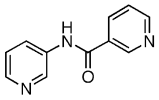
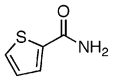
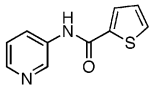
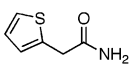
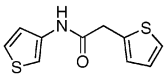
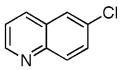
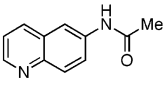
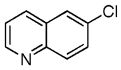
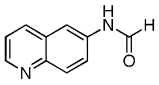
Although heteroaromatic amides are important biologically active compounds,[11] only a few examples of Pd-catalyzed amidations using these substrates have been reported.[3h,12] Consequently, the optimized conditions were applied to the amidation of heteroaromatic chlorides (Table 3). We found that both aliphatic (entries 1, 5, and 6) and aromatic (entries 3 and 4) amides, as well as formamide (entries 2 and 7), can be coupled with heteroaryl chlorides to afford heteroaromatic amides in good to excellent yields.

Aryl and heteroaryl bromides, triflates, and tosylates[2c] can also be efficiently combined with a variety of amides (Table 4). Aryl bromides can be selectively coupled with acetamide in the presence of a competing aryl chloride (entries 1 and 2). The ability to utilize aryl tosylates further increases the substrate scope for this catalytic system (entries 8 and 9).[2c]

As we were intrigued about the reason(s) for the superiority of **6** in promoting a wide range of amidation reactions, we used *in situ* IR spectroscopy to monitor several amidation reactions employing various ligands. First, in order to test the stability of the catalytic system based upon **6**, we monitored the formation of amidation product under two sets of conditions (Figure 1). In run 1, chlorobenzene (1.5 mmol) and benzamide (1.8 mmol) were allowed to react using Pd_2dba_3 (0.0075 mmol)

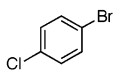
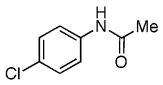
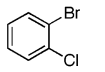
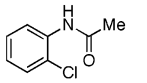
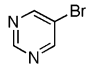
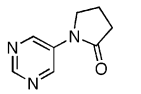
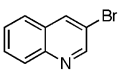
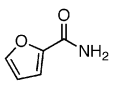
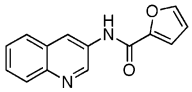
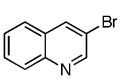
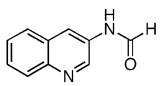
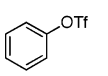
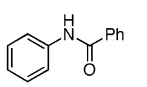
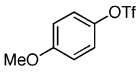
(11) (a) Nayyar, A.; Malde, A.; Jain, R.; Coutinho, E. *Bioorg. Med. Chem.* **2006**, *14*, 847−856. (b) Raju, S.; Kumar, P. R.; Mukkanti, K.; Annamalai, P.; Pal, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6185−6189. (c) Amin, K.; Broddefalk, J.; Desfosses, H.; Evertsson, E.; Liu, Z.; Milburn, C.; Nilsson, K.; Tremblay, M.; Walpole, C.; Wei, Z.-Y.; Yang, H. WO 2005115986.
(12) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433−2435.

Table 3. Pd-Catalyzed Coupling of Heterocyclic Aryl Chlorides with Amides[a]

Entry	ArCl	Amide	Product	Pd (mol %)	Yield (%)[b]
1				1	99
2				2	75
3				1	97
4				1	94
5				2	85
6				1	90
7				2	85[c]

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.0−1.5 equiv of amide, 1.2−1.5 equiv of K_3PO_4, *t*-BuOH ([aryl chloride] = 0.5 M), Pd_2dba_3 (0.5−1.0%), Ligand **6** (2.5−5%) (Pd/L = 1/2.5). [b]Yields represent isolated yields of compounds estimated to be ≥95% pure as judged by ^{1}H NMR, GC, and combustion analysis (average of two runs). [c]K_2CO_3 and Ligand **5** were used.

Table 4. Pd-Catalyzed Coupling of Aryl Bromides and Sulfonates with Amides[a]

Entry	ArX	Amide	Product	Pd (mol %)	Yield (%)[b]
1				1	81
2				2	68
3				2	88
4				1	60[c]
5				2	84
6				1	99
7				1	95
8				2	99
9				2	92[d]

[a] Reaction conditions: 1.0 equiv of aryl halide/pseudohalide, 1.0−1.5 equiv of amide, 1.2−1.5 equiv of K_3PO_4, *t*-BuOH ([aryl bromide or aryl sulfonate] = 0.5 M), Pd_2dba_3 (0.5−1.0%), Ligand **6** (2.5−5%) (Pd/L = 1/2.5). [b]Yields represent isolated yields of compounds estimated to be ≥95% pure as judged by ^{1}H NMR, GC, and combustion analysis (average of two runs). [c]Because of difficult purification, the product was isolated in relatively low yield. [d]Molecular sieves (3 Å) were used.

and **6** (0.01875 mmol). In run 2, chlorobenzene (0.5 mmol) and benzamide (0.8 mmol) were employed with Pd_2dba_3 (0.0075 mmol) and **6** (0.01875 mmol). The kinetic profiles of these two systems show excellent overlap, which implies that significant catalyst decomposition does not occur during the course of the reaction.[13,14] Additionally, the overlapping curves indicate that the same quantity of active catalyst is present in both systems. Thus, although the catalytic system based on **6** is extremely reactive, it is also stable. The stability of this catalytic system permits (as demonstrated in Table 2, entry 2) the use of relatively low levels of catalyst without a negative effect on isolated yield.

Because it has been difficult to obtain structural information on intermediate complexes in the catalytic cycle, we turned to computational chemistry in order to determine the role of the ligand in amidation reactions using dialkylbiaryl phosphine ligands. Using *all-atom* DFT,[15] we optimized several structures of the type L_1Pd(Ph)(acetamidate), where L = **5** and **6**. Additionally, we postulated that only the methyl group *ortho* to the phosphorus center in **6** is required to efficiently promote Pd-catalyzed amidation reactions. Hence, we also performed a geometry optimization on **7**•Pd(Ph)(acetamidate), where **7** is 2-di-*tert*-butyl-(2′,4′,6′-triisopropyl)-3-methylbiphenyl. From these structures (**A**−**D**), it is clear that the most favored geometry around the Pd center is that with the acetamidate *trans* to the phosphorus, regardless of the ligand employed (Figure 2). Three of these structures (**A**, **B**, and **D**) contain an amidate bound to Pd(II) via the nitrogen of the amidate. However, compound **C** contains a κ^2-bound amidate, which has previously been proposed to inhibit reductive elimination and/or catalyst activation.[6]

We postulated that the methyl group *ortho* to the phosphorus center in **6** and **7** (corresponding to **A** and **D**) may inhibit rotation of the palladium center to a κ^2-amidate geometry such as that in **C**. In order to determine the extent to which the *ortho* methyl group inhibits rotation of the palladium center to a geometry that allows formation of a κ^2-amidate, we undertook a potential energy scan varying the C1−C2−P−Pd dihedral angle from 180° to 40° (step size of 10°) in complexes **B** and **D** (Chart 1). The most striking feature of Chart 1 is the relative energies of the global maxima, which correspond to the activation energy of rotation about C2−P, for complexes **B** and **D**. From these data, $\Delta G^{\ddagger} \approx 17$ kcal/mol for rotation around the C2−P bond in complex **B**, while $\Delta G^{\ddagger} \approx 33$ kcal/mol for an analogous rotation in complex **D**. These values strongly suggest that the *ortho* methyl group in ligands **6** and **7** does indeed play a significant role in inhibiting rotation around C2−P in complexes **B** and **D** to complexes that could potentially possess a κ^2-amidate. Specifically, rotation around C2−P in **D** is likely

(13) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302−4320.
(14) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584−3591.
(15) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183−2192.

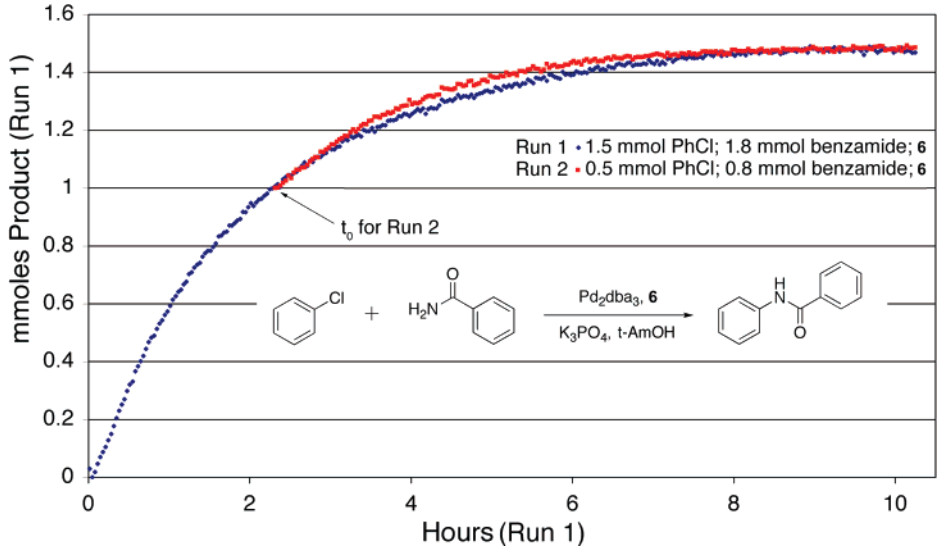


Figure 1. Overlay of *in situ* IR kinetic traces of the coupling of chlorobenzene and benzamide with **6** under different conditions for the determination of catalyst stability.

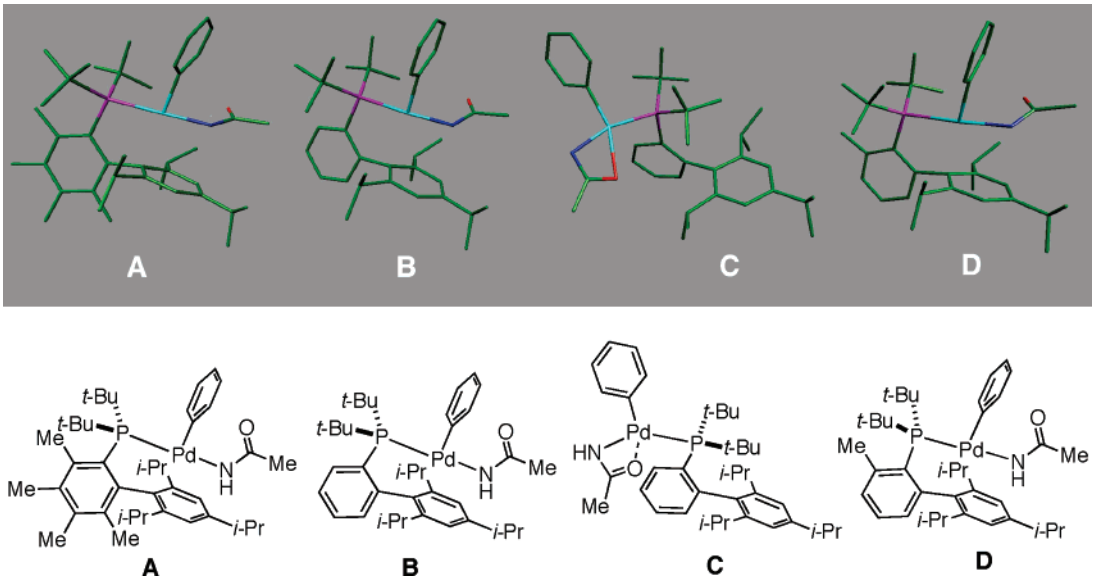


Figure 2. Optimized local minima for the monoligated LPd(Ph)(acetamidate) complexes (phosphorus in purple, palladium in turquoise, nitrogen in blue, oxygen in red). In structure A, L = **6**; in structures B and C, L = **5**; in structure D, L = **7**.

not viable under any reaction conditions employed in our work, since the rate constant for rotation around C2−P in complex **D** is on the order of 1.2×10^{-6} s^{-1}at 110 °C, while the rate constant for rotation around C2−P in complex **B** is on the order of 1.6×10^{3} s^{-1} at 110 °C. Hence, the lack of an *ortho* methyl group, as in ligand **5**, allows for rotation around C2−P to occur rapidly, which thereby allows for the formation of the κ^2-amidate (**C**). It is important to note here that we assume that complexes **B** and **D** exist in the geometry depicted in Chart 1 based upon the X-ray crystal structure of **5** which positions the lone pair of electrons on phosphorus proximal to the non-phosphine ring of the ligand. We anticipate that the Pd center binds the phosphorus center in the conformation depicted in the X-ray crystal structure of **6** and remains proximal to the non-phosphine-containing ring of the ligand during oxidative addition and displacement of the chloride ligand by the amidate. This assumption is based upon the above data that demonstrate that the methyl group *ortho* to the phosphorus center in both **6** and **7** inhibits rotation around C2−P.

In order to corroborate the importance of the methyl substituent *ortho* to the dialkylbiarylphosphino group, **7** was prepared. For amidations employing **7**, isolated yields were nearly identical to those achieved using **6** (e.g., when **7** was used instead of **6** in entry 6 in Table 1, a 95% yield was obtained). In addition, using *in situ* IR spectroscopy, the kinetic profiles of cross-coupling processes employing **6** and **7** were shown to be very similar (Figure 3). Thus, consistent with the computational model, the efficiency of amidations using **6** appears to stem directly from the addition of a single methyl group to the upper biphenyl ring of **5**. When ligand **5**, which does not possesses an *ortho* methyl group, was employed in the cross-coupling of chlorobenzene and benzamide, a greater initial rate was observed, but the reaction only proceeded to

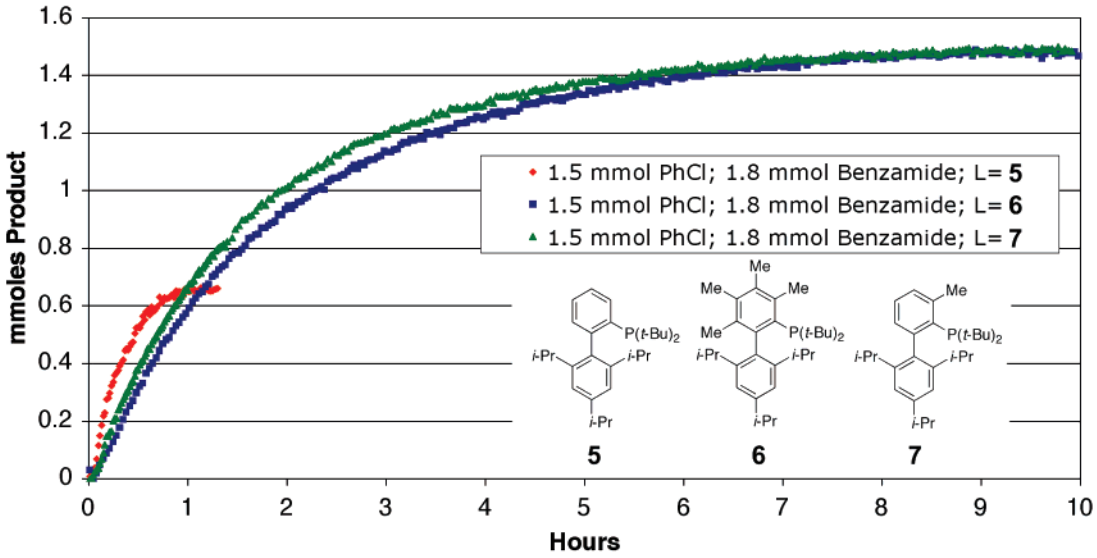
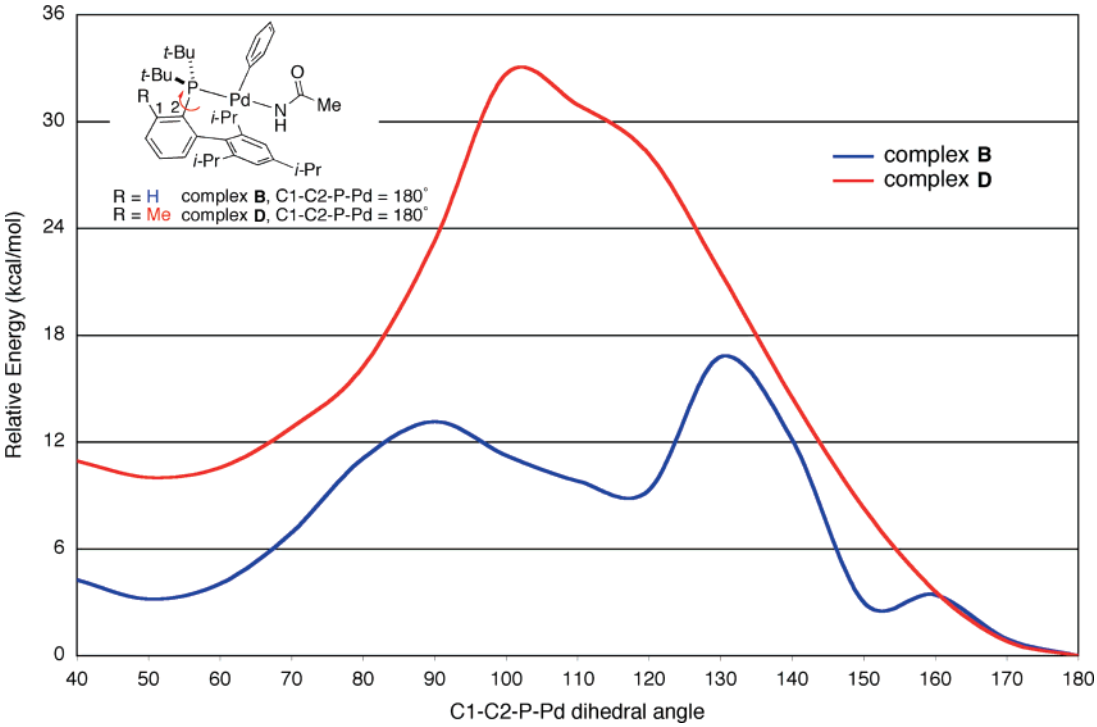


Figure 3. *In situ* IR kinetic traces for the coupling of chlorobenzene and benzamide using ligands **5**, **6**, and **7**.

Chart 1. Potential Energy Surface (PES) Scan of Complexes **B** and **D** Illustrating the Energy Required for Rotation around C2−P To Allow for the Formation of a κ^2-Amidate Complex

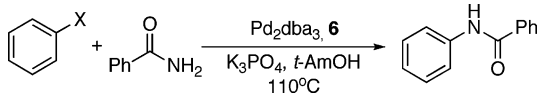


∼40% conversion of chlorobenzene and the formation of palladium black was clearly visible (Figure 3). In contrast to this result, catalyst systems based on **6** show only nominal decomposition over the same time frame (Figure 1). Although we are uncertain of the specific decomposition mechanism of catalyst systems based on **5**, we hypothesize that palladium black formation results from the self-catalytic aggregation of palladium clusters.[16] It is possible that these clusters form via a pathway that involves a κ^2 intermediate. It has previously been shown that κ^2-amidate complexes decompose with little formation of amide product, though the identity of the decomposition product(s) has not been identified.[6] As described above, the formation of a κ^2-amidate is calculated to be suppressed when using **6** or **7**. Although **6** and **7** provide nearly identical reaction profiles, **6** is the preferred ligand due to the difficulty in preparing **7** caused by the formation of regioisomers.

Further *in situ* IR spectroscopy studies demonstrated that the rate of the reaction is highly dependent upon the nature of the aryl halide/pseudohalide. The kinetic profiles for coupling reactions demonstrate that the initial rate for the amidation of phenyl triflate with benzamide is very rapid (6.55×10^{-3} mmol/s), while those of bromobenzene (1.30×10^{-3} mmol/s) and chlorobenzene (2.3×10^{-4} mmol/s) show successive decreases in initial rate (Table 5). These results suggest that reductive

(16) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285−3288.

Table 5. Observed Initial Rates for Pd-Catalyzed Couplings of Phenyl Halides/Triflate with Benzamide[a]



entry	X	equiv of PhX	initial rate[b] (×10^{-4} mmol/s)
1	Cl	0.25	0.6
2	Cl	0.5	1.2
3	Cl	1	2.3
4	Cl	2	4.0
5	Cl	3	5.4
6	Cl	5	7.3
7	Br	1	13.0
8	Br	2	15.6
9	OTf	1	65.5
10[c]	OTf	1	8.5
11[d]	OTf	1	67.7
12	OTf	2	68.1

[a] Reaction conditions: 1.5 mmol of aryl halide/triflate, 1.8 mmol of benzamide, 2.25 mmol of K_3PO_4, 3 mL of *tert*-amyl alcohol, 0.5 mol % Pd_2dba_3, 2.5 mol % **6**. [b] Average of two runs. [c] With 1.8 mmol of Bu_4NCl. [d] With 1.8 mmol of Bu_4NOTf.

elimination from the amidate complex is not the turnover-limiting step of the catalytic cycle, as the reaction rate is highly dependent on the nature of the halide/pseudohalide. If reductive elimination were indeed the rate-limiting step in Pd-catalyzed amidation reactions, the reaction rate would likely be independent of the nature of the halide/pseudohalide. We suggest that since benzamide reacts 5-fold faster with phenyl triflate than with bromobenzene, the coordination of benzamide and/or attack of benzamidate on the Pd(II) oxidative addition species influences the rate of reaction. Coordination of benzamide and/or attack of benzamidate on the Pd(II) oxidative addition species would be more rapid with the LPd(Ph)OTf complex relative to the LPd(Ph)Br complex due to the cationic nature of the palladium center in LPd(Ph)OTf.[17] Further support that coordination of benzamide and/or attack of benzamidate on the Pd(II) oxidative addition complex may influence the overall rate of the reaction is provided by a prior report by Hartwig which demonstrates that reductive elimination from Xantphos−Pd(Ph)(PhNC(O)Me) is relatively facile (93% yield of product is obtained after 7 h at 90 °C).[6] Although this stoichiometric reaction readily occurs, we have previously found that the catalytic reaction only provides product in <10% yield (the reaction of PhBr with acetanilide, catalyzed by Xantphos/Pd_2dba_3). Since it is well-known that Pd catalysts based upon Xantphos undergo oxidative addition with PhBr, it is clear that this step is not causing the catalytic reaction to fail. Hence, the problematic step in the catalytic reaction of PhBr and acetanilide catalyzed by Xantphos is likely the binding of the amide and/or the attack of the amidate on the Pd(II) oxidative addition species. While Xantphos does indeed catalyze various Pd-amidation reactions, we propose that this particular reaction fails due to the reduced nucleophilicity of acetanilide relative to other smaller, more electron-rich amides in combination with the fact that the Xantphos−Pd(Ph)Br complex is coordinatively saturated (i.e., two phosphines, one phenyl group, and one bromide). Additionally, these results are consistent with the difficulty in coupling *ortho* substituted aryl chlorides with amides. Although oxidative addition can readily occur with hindered aryl chlorides, the "transmetallation" step is likely slowed due to the added bulk of the arene bound to the Pd(II) oxidative addition complex.

Finally, only a small change in initial rate is observed when the concentration of PhBr or PhOTf is doubled. These data suggest that the rate-limiting step occurs following oxidative addition in amidations using aryl bromides and triflates. When the number of equivalents of PhCl employed in the cross-coupling is increased, saturation is observed (entries 1−6). This is consistent with two possible scenarios: (1) reversible oxidative addition of PhCl[18] or (2) comparable rates (and rate constants) of oxidative addition and "transmetallation" such that, at low concentrations of PhCl, oxidative addition is rate-limiting while, at high concentrations of PhCl, "transmetallation" becomes rate-limiting.

When 1.2 equiv of tetrabutylammonium chloride are added to the coupling of PhOTf and benzamide (entry 10), the rate of the reaction slows dramatically. Since the oxidative addition of PhOTf should not be slowed by the addition of exogenous chloride, this result supports our suggestion that "transmetallation" is the rate-limiting step in this catalytic system. When an analogous reaction is conducted, employing non-nucleophilic Bu_4NOTf to control the ionic strength, only a nominal change in rate is observed (entry 11) compared to the original coupling without the tetrabutylammonium additive (Entry 9).

Conclusion

In conclusion, we have demonstrated the ability of a finely tuned, monodentate, biaryl phosphine to promote the efficient catalytic amidation of aryl chlorides. The use of DFT and kinetic studies further elucidated the importance of the ligand architecture. Our results are in accord with a previous report that suggests that the formation of κ^2-amidate complexes is deleterious to the effectiveness of a catalyst for Pd-catalyzed amidation reactions. Kinetic data are provided that suggest that either oxidative addition (at low concentrations of PhCl) or "transmetallation" is the rate-limiting step in this catalytic system. Additionally, DFT and kinetic studies suggest that the addition of a single methyl group to the upper phenyl ring of a phosphine is the source of the enhanced stability of the catalytic system. As a result, a ligand that has typically been ineffective in the amidation of aryl chlorides was converted into a ligand that creates a stable, yet highly active, catalyst capable of the amidation of a large range of aryl halides and aryl sulfonates.

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Supporting Information Available: Experimental procedures and spectral data for all compounds, computational data, kinetic plots, and X-ray data for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Displacement of X from complexes of the type L•Pd(X) (where X = halide or triflate) is more facile in palladium triflate complexes than palladium halide complexes. For example, see: Oliver, D. L.; Anderson, G. K. *Polyhedron* **1992**, *11*, 2415−2420.

(18) (a) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533−1541. (b) Roy, A. H.; Hartwig. J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944−13945. (c) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233.