A Second-Generation Catalyst for Aryl Halide Amination: Mixed Secondary Amines from Aryl Halides and Primary Amines Catalyzed by (DPPF)$PdCl_2$

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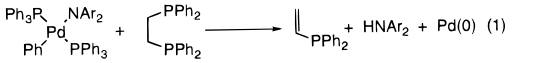
Received March 22, 1996

Aromatic amines are important substructures in natural products and organic materials.[1−3] Our group[4] and Buchwald's[5] have recently reported the palladium-catalyzed amination of aryl halides in the presence of alkoxide and amide bases that significantly improved upon amination procedures employing toxic and air sensitive aminostannanes.[6,7] Although these methods gave high yields with secondary amines and aryl bromides, a general, high-yielding intermolecular amination procedure involving primary amine substrates or aryl iodide electrophiles[8] had not been developed. The catalysts used for intermolecular aminations contained tri-*o*-tolylphosphine as the ligand. Our mechanistic studies have shown that each complex on the reaction coordinate involving this catalyst is a monomeric, monophosphine species.[9−13] The large size of this ligand leads to fast reaction rates by favoring low coordination number compounds and high selectivity for arylamine formation by favoring reductive elimination of arylamine over β-hydrogen elimination of imine.[14]

Our studies of late-transition metal amido complexes have now led to a second-generation aryl halide amination catalyst, (DPPF)$PdCl_2$ (DPPF = 1,1′-bis(diphenylphosphino)ferrocene), which is based on chelating ligands. This catalyst provides high yields of mixed, secondary arylamines from aryl halides and primary amines, examples that gave low to moderate yields with the tri-*o*-tolylphosphine system. In addition to the practical advantages of this system, these results reveal a number of important concepts: (1) the catalytic cycle involves bis(phosphine) intermediates; (2) sterically encumbered phosphines are not necessary for high-yielding, intermolecular amination of aryl halides; (3) the favorable selectivity for reductive elimination over β-hydrogen elimination results from chelation and large bite angle, rather than from steric effects; (4) a wide range of chelating ligands may lead to optimization of reaction rates and yields. We report the aryl halide amination chemistry of DPPF-ligated palladium complexes and the transition metal−amido chemistry that led us to this system.

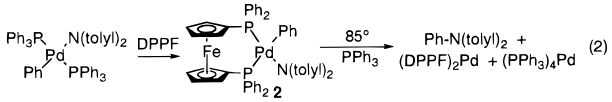
Recently, we sought the preparation of palladium amido complexes containing chelating ligands in order to evaluate their potential as intermediates in amination chemistry that might display higher turnover numbers, greater compatibility with functional groups, and greater stability toward displacement by primary amines. Our most recent kinetic results on the reductive elimination of arylamines from $[Pd(PPh_3)_2(NAr_2)(Ph)]$[15] demonstrated that a reductive elimination pathway involving a four-coordinate intermediate can occur in competition with reductive elimination from three-coordinate intermediates.[16] Further, independent studies from our group on the β-hydrogen elimination of $[Ir(CO)(PPh_3)_2(NRAr)]$ complexes showed that the β-hydrogen elimination of square planar, transition metal amides requires a 14-electron intermediate.[17] These results implied that the presence of chelating ligands would inhibit β-hydrogen elimination more than reductive elimination and would, therefore, improve the selectivity for amination vs reduction.

Despite these kinetic results, the general chemistry of palladium amido aryl complexes with chelating ligands was dominated by reactions other than C−N bond-forming reductive elimination. For example, addition of DPPE (1,2-bis(diphenylphosphino)ethane) to a solution of the previously reported PPh_3-ligated amido complex $(PPh_3)_2Pd(Ph)[N(tolyl)_2]$ (**1**) led to decomposition of the ligand backbone by P−C bond cleavage and formation of vinyldiphenylphosphine in 93% yield, as shown in eq 1.[18] Addition of other chelating ligands such as DPPP (1,2-bis(diphenylphosphino)propane), DPPBz (1,2-bis(diphenylphosphino)benzene), and DPPEn (1,2-bis(diphenylphosphino)ethylene) did not produce stable amido complexes, and no arylamine products were observed.



(1)

Nevertheless, we found that amido complexes containing the DPPF ligand could be isolated or observed spectroscopically and that these complexes produced arylamines in high yields by reductive elimination. As shown in eq 2, addition of DPPF to **1** generated (DPPF)Pd(Ph)[$N(tolyl)_2$] (**2**) in 54% yield, and this complex underwent high-yielding reductive elimination of amine when warmed to 85 °C in the presence of free PPh_3.



(2)

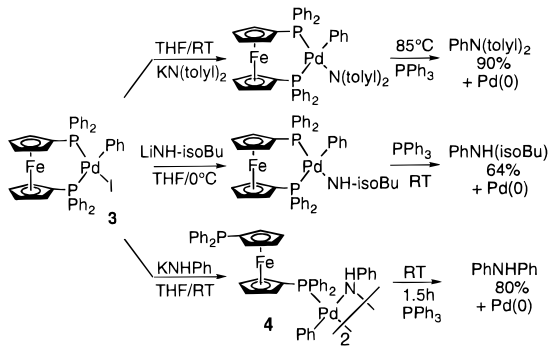
On a preparative scale, **2** was formed by addition of $KN(C_6H_4\text{-}p\text{-}Me)_2$ to (DPPF)Pd(Ph)I (**3**)[19] at room temperature in THF and was isolated in 69% yield by addition of pentane to a concentrated toluene solution. The complex displayed two sharp doublets in the $^{31}P\{^1H\}$ NMR spectrum, demonstrating the *cis*, four-coordinate geometry in Scheme 1. The $^{31}P\{^1H\}$ NMR chemical shifts of **2** were located downfield of those for aryl halide complex **3**. Warming a benzene-d_6 solution of **2** at 85 °C in the presence of free PPh_3 induced the formation of Ph-$N(tolyl)_2$ in 90% yield by ^1H NMR spectroscopy involving an internal standard. $(DPPF)_2Pd$ and $(PPh_3)_4Pd$ were the only transition metal products observed by ^{31}P NMR spectroscopy.

Substitution chemistry also allowed for the observation of DPPF-ligated palladium primary amides, and these complexes underwent facile reductive elimination of mixed secondary amines at room temperature or below. For example, addition of LiNH^{i}Bu to a THF solution of **3** at low temperature (0 °C) resulted in the formation of a new species, which displayed two doublets in the ^{31}P NMR spectrum (26.5, 18.3 ppm, J = 22.0 Hz). The ^{31}P chemical shifts of this product were located

(1) Buckingham, J. *Dictionary of Natural Products*, 1st ed.; University Press: Cambridge, MA, 1994.
(2) Negwer, M. *Organic-Chemical Drugs and Their Synonyms (an international survey)*, 7th ed.; Akademie Verlag GmbH: Berlin, 1994.
(3) D'Aproano, G.; Schiavon, G.; Zotti, G.; Leclerc, M. *Chem. Mater.* **1995**, *7*, 33−42.
(4) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
(5) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.
(6) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927−928.
(7) Kosugi, M.; Kameyama, M.; Sano, H.; Migita, T. *Nippon Kagaku Kaishi* **1985**, *3*, 547−551.
(8) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135.
(9) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
(10) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.
(11) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.
(12) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598.
(13) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics*, in press.
(14) Hartwig, J. F.; Richards, S. *J. Am. Chem. Soc.* **1996**,
(15) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708−4709.
(16) Driver, M. S.; Hartwig, J. F. Unpublished results.
(17) Recent studies have indicated that β-hydrogen elimination requires an open coordination site. Hartwig, J. F. *J. Am. Chem. Soc.*, in press.
(18) This phosphine is commercially available. The ^1H NMR, GC retention time, and GC/MS were compared to an authentic commercial sample.
(19) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249.

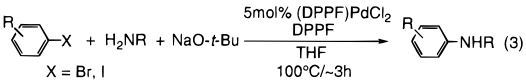
S0002-7863(96)00937-7 CCC: $12.00

Scheme 1



downfield of those for **3**, in a similar fashion to the downfield shifts of isolated **2**. Given the clean reactivity of potassium amides with **3** to give **2** and the similarity in ^{31}P chemical shifts, the reaction product formed at low temperature is presumably the *cis*-ligated isobutylamido aryl complex. Consistent with this proposal, PhNH^{i}Bu was formed in 64% yield upon warming to room temperature.[20] A new palladium amido complex **4** was also formed upon addition of KNHPh to a THF solution of aryl halide **3**. The ^{31}P NMR spectrum of this complex contained two singlets (22.3, −16.6 ppm), the upfield signal falling in the region of free DPPF. The absence of coupling between the two P atoms and the similarity of one resonance to that of free DPPF suggested that this species was the dimeric palladium anilide shown in Scheme 1. Again, the DPPF amido complex underwent reductive elimination of amine at or below room temperature. Ph-NHPh formed from **4** in 80% yield after standing at room temperature for 1.5 h in the presence of added PPh_3.[20]

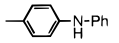
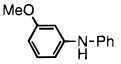
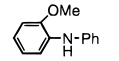
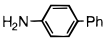
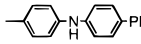
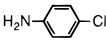
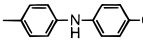
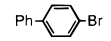
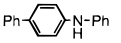
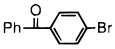
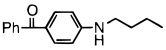
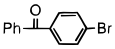
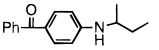
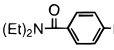
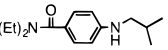
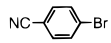
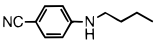
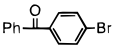
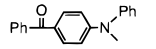
The observation of these facile reductive elimination reactions, particularly in the case of primary amines containing β-hydrogens, led us to test DPPF-ligated palladium complexes as catalysts for the formation of aromatic secondary amines by reaction between primary amines and aryl halides. Indeed, (DPPF)$PdCl_2$ (**5**)[21] proved to be an effective catalyst for the amination of aryl bromides and iodides with both aryl and alkyl primary amines (eq 3). A summary of the catalytic reactions



conducted with **5** is provided in Table 1.[22]

As shown in Table 1, reactions of aryl halides and primary amines catalyzed by **5** provided a general route to a variety of aryl amines in high yields. The efficient reaction of aryl iodides, as well as aryl bromides, extends the scope of amination reactions to a wider range of electrophiles. Aryl halides with either electron-donating or electron-withdrawing substituents, as well as those bearing ortho substituents (entry 3), reacted effectively with anilines after only 3 h. Both primary aryl- and alkylamines reacted in high yields with aryl halides containing an electron-withdrawing group.[23] These yields are improved

Table 1. (DPPF)$PdCl_2$-Catalyzed Reactions of Aryl Halides with Primary Amines[a]

Entry	ArX	Amine	Product	Work-up[b]	Yield[c]
1				A	92%
2				A	92%
3				B	96%
4				A	80%
5				A	84%
6				A	94%
7				B'	96%
8				B'	84%
9				B	82%
10				B	93%
11				B	87%

[a] Reactions conducted in THF solvent at 100 °C for 3 h. [b] Workup A: product isolated by sublimation. Workup B: product isolated by silica-gel chromatography using 10:1 hexanes/ether follwed by 4:1 hexanes/ether as eluting solution. Workup B′: products isolated by silica-gel chromotography using 20:1 hexanes/EtOAc as eluting solution. Details included in supporting information. [c] Yields reported correspond to isolated compounds that were pure by NMR spectroscopy and by microanalysis when submitted.

substantially over similar examples involving the P(*o*-tolyl)$_3$-based catalysts.[5,8] The use of a secondary amine (entry 11) was successful in the case of an *N*-alkyl arylamine after only a 3 h reaction time. However, attempts to use dialkylamines led to the formation of arene products. The use of secondary aminostannanes also resulted in the formation of arene products.

In conclusion, we present the generation and reductive elimination of DPPF-ligated palladium amido complexes that suggested the use of (DPPF)$PdCl_2$ as a catalyst for the formation of mixed secondary arylamines from aryl halides. The yields of such reactions are improved significantly over those involving P(*o*-tolyl)$_3$-ligated catalysts. Since the DPPF is much smaller than P(*o*-tolyl)$_3$, the difference in reactivity is clearly rooted in coordination number and geometry rather than steric bulk. Thus, a wide range of ligands should be considered for this catalytic chemistry, and four-coordinate, bis(phosphine) complexes can serve as intermediates in such aminations.

Acknowledgment. We gratefully acknowledge a DuPont Young Professor Award, a National Science Foundation Young Investigator Award, the Exxon Education Foundation, and a Dreyfus Foundation New Faculty Award for support for this work. J.F.H. is a fellow of the Alfred P. Sloan Foundation. We would also like to thank Johnson-Matthey Alpha/Aesar for donation of palladium chloride. We thank Professor Stephen L. Buchwald for sharing his unpublished results and for an exchange of manuscripts.

Supporting Information Available: Spectroscopic and analytical data for **2**, specific amination procedures for entries 5 and 7, general workup procedures, and spectroscopic data and copies of NMR spectra for organic products (25 pages). See any current masthead page for ordering and Internet access instructions.

JA960937T

(20) The only palladium products seen at the end of reaction were $(DPPF)_2Pd$ and $(PPh_3)_4Pd$.

(21) **5** was made prepared as an air-stable red crystalline solid by a method analogous to that for (DPPE)$PdCl_2$. Davies, J. A.; Hartley, F. R.; Murray, S. G. *J. Chem. Soc., Dalton Trans.* **1979**, 1705.

(22) In an inert atmosphere dry box, (DPPF)$PdCl_2$ and 3.0 equiv of DPPF/Pd were added to a solution of 20 equiv of bromobenzophenone and 25 equiv of sodium *tert*-butoxide in 8 mL of anhydrous THF. The reaction tube was sealed with a cap containing a PTFE septum and removed from the dry box. Butylamine (25 equiv) was added to the reaction mixture by syringe, and the mixture was heated at 100 °C for 3 h. The reaction was cooled to room temperature, the volatile materials were removed by rotary evaporation, and the product was isolated by either sublimation or silica-gel chromatography (20:1 hexane/EtOAc or 10:1 hexane/Et_2O followed by 4:1 hexane/Et_2O).

(23) Data in the accompanying paper by Buchwald et. al. shows that diarylation of unhindered alkyl amines can occur in the case of electronically neutral aryl halides: Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 0000.