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Phospha-adamantanes as ligands for organopalladium chemistry: aminations of aryl halides

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Abstract—The use of $Pd_2dba_3{\cdot}CHCl_3$ and 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane has been shown to facilitate the effective amination of aryl halides with aromatic or aliphatic amines in high yields.

The palladium-catalyzed amination of aryl or heteroaryl halides represents one of the most versatile methods for the preparation of functionalized anilines.[1] In recent years, the scope of this reaction has been enhanced as a result of the utilization of new phosphine ligands that permit these aminations to take place under milder conditions and with reaction partners that did not previously participate in coupling.[2] Indeed, many other organopalladium coupling reactions have benefited from the incorporation of bulky, electron-rich phosphine ligands in their catalyst systems.[3] For example, our work involving the development of new ligands based on a phospha-adamantane framework has allowed for Suzuki cross-coupling of a variety of aryl halides and boronic acids under mild conditions.[4] This same ligand (Fig. 1, R = Ph) can also be used for solid-phase Suzuki couplings involving immobilized reaction partners.[5] In addition, an air stable palladium complex of this phenyl-phospha-adamantane ligand has been shown to be an effective, versatile catalyst for use in the Suzuki and Sonogashira reactions and the α-arylation of ketones.[6] In an effort to determine and expand the scope of applicability of the phospha-adamantane ligand, the present paper describes the use of $Pd_2dba_3{\cdot}CHCl_3$ and 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (PA-Ph) to facilitate the amination of aryl halides.

Initial screening revealed that optimum yields could be achieved using $Pd_2dba_3{\cdot}CHCl_3$ (and to a lesser extent $Pd(OAc)_2$) as the catalyst, toluene as the solvent (although reasonable yields could be achieved in pentane as well) and sodium *tert*-butoxide (or potassium *tert*-butoxide) as the base. A screening of three phospha-adamantane ligands (Fig. 1, R = Ph, 2-tolyl or $C_{14}H_{29}$)[4] revealed that each was capable of affecting the amination reaction with comparable efficiency. Optimization was carried out using the more readily accessible phenyl-phospha-adamantane ligand (PA-Ph). Finally, loadings of 2% $Pd_2dba_3{\cdot}CHCl_3$ with 4% PA-Ph (to give a Pd to ligand ratio of 1:1) allowed for excellent yields in a reasonable amount of time.

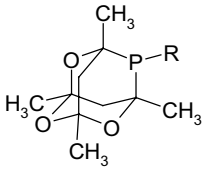

Figure 1.

With the ideal conditions in hand,[7] an array of amines and aryl halides were coupled. As seen in Table 1, diaryl- (entries 1–3), aryl/alkyl- (entries 4–7), cyclic dialkyl- (entries 10–15) and acyclic dialkyl-amines (entries 16 and 17) could be smoothly coupled to deactivated or more sterically demanding aryl iodides (at 30 °C), bromides (at 50 °C) or chlorides (at 70 °C) in high yields. Reactions involving aniline (entries 8 and 9) could be carried out but required elevated temperatures (90 °C for bromides and 110 °C for chlorides) for excellent conversions. Reactions involving primary aliphatic amines

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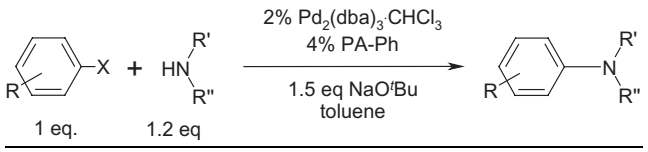
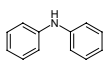
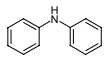
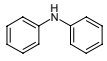
Table 1. Aminations of aryl halides



Entry[8]	Amine	Aryl halide	Yield[a] (%)		
			X = I[b]	X = Br[c]	X = Cl[d]
1			96	94	
2				95	
3			93	97	94
4			95	97	
5			94	96	
6				96	94
7			92	97	96
8				94[e]	92[f]
9				91[e]	94[f]
10			97	94	
11				97	96
12			97	98	95
13				94	97
14			94	93	97
15[9]				96	
16[9]			97	98	
17[9]				97	96

[a] Average isolated yield of two runs.
[b] 30 °C, 5–10 h.
[c] 50 °C, 10–20 h.
[d] 70 °C, 5–22 h.
[e] 90 °C, 24 h.
[f] 110 °C, 24 h.

allowed for the production of only trace amounts of products as detected by GC/MS analysis. These negative results are inconsistent with those published in the literature, where modest yields have been reported. Work in this area is continuing.

Overall, the methodology developed describes a versatile, simple method for the amination of aryl halides and compares favourably with those previously described while offering a number of distinct advantages. The phenyl-phospha-adamantane ligand is crystalline, air-stable, can be recovered by chromatography and reused. The catalytic system allows for a robust, reproducible reaction that does not require any special handling. Further applications of the ligand in organopalladium chemistry are under development.

Acknowledgements

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6. Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082.
7. General palladium-catalyzed amination protocol: $Pd_2(dba)_3 \cdot CHCl_3$ (2%, 20.7 mg, 0.02 mmol), 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (4%, 11.7 mg, 0.04 mmol), sodium *tert*-butoxide (144 mg, 1.5 mmol), the amine (1.2 mmol) and the aryl halide (1.0 mmol) were stirred in toluene (dry, degassed, 1.5 mL) under an argon atmosphere and heated (at 30 °C for aryl iodides, 50 °C for aryl bromides or 70 °C for aryl chlorides). Note that elevated temperatures are required for couplings involving aniline (90 °C for bromides and 110 °C for chlorides). The reaction was monitored via TLC and after the appropriate amount of time, the reaction was then diluted with diethyl ether (10 mL), washed with distilled water (1×10 mL) and brine (1×10 mL). The organic solution was concentrated under reduced pressure and the residue purified via flash silica gel chromatography.
8. Spectroscopic data is identical to that previously published: entries 1, 2, 3, 4, 6, 7 and 8 see: Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553; entry 5 and 14 see: John, P.; Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133; entry 9 see: Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*,

6479; entry 10 and 12 see: Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829; entry 11 see: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144; entry 13 see: Belfield, A. J.; Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron* **1999**, *55*, 13285.

9. Spectroscopic data for entry 15: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.87 (6H, s), 3.04 (4H, m), 3.85 (4H, m), 6.75 (2H, d), 6.87 (2H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.6, 51.1, 67.2, 114.5, 118.0, 143.2, 145.9. For entry 16: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (6H, t), 1.56 (4H, m), 2.22 (3H, s), 3.17 (4H, t), 6.56 (2H, d), 6.99 (2H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 20.2, 20.5, 53.1, 112.1, 124.3, 129.7, 146.2. For entry 17: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (6H, t), 1.61 (4H, m), 3.27 (4H, t), 6.57 (2H, d), 7.42 (2H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 20.2, 52.7, 96.3, 111.1, 121.0, 133.6, 150.7.