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General and Efficient Catalytic Amination of Aryl Chlorides Using a Palladium/Bulky Nucleophilic Carbene System

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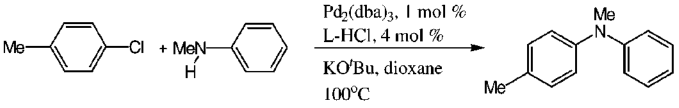
ABSTRACT



A combination of palladium and an imidazolium chloride has been used as catalyst precursor in the amination of aryl chlorides. The imidazolium salt IPrHCl (4, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) was found to provide the most efficient transformation rates in this catalytic system. This new system proves general and efficient for aryl chlorides as well as aryl bromides and iodides.

Palladium-catalyzed cross-coupling reactions of aryl halides or halide equivalents with various nucleophiles have been shown to be highly effective and practical methods for the formation of C−C bonds.[1] In a closely related area, palladium- or nickel-mediated coupling of aryl halides with amines has attracted significant interest because of the use of this methodology in organic synthesis and material science.[2] The pioneering studies of Hartwig and Bulchwald on catalytic amination have shown that the supporting ligands on the metal center play a crucial role in dictating the efficiency of the catalytic system.[2] To this end, bulky monodentate phosphine or bidentate PX (X = P, N, O) ligands are usually employed.[3,4] Most recent examples deal with Suzuki[3a] and Stille[4a] coupling reactions.

Nucleophilic *N*-heterocyclic carbenes,[5] or so-called "phosphine mimics", have attracted considerable attention as possible alternatives for the widely used phosphine[6] ligands in homogeneous catalysis.[7,8] The primary advantage of these ligands appears to be that they do not easily dissociate from the metal center, and as a result an excess of the ligand is not required in order to prevent aggregation of the catalyst usually affording the bulk metal.[9] The use of some of these ligands in palladium-catalyzed Heck and Suzuki reactions,[10,11] rhodium-assisted hydrosilylation,[12] and ruthenium-

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(1) (a) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, pp 799−938. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985. (c) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995. (d) Tsuji, J. *Synthesis* **1990**, 739−749.

(2) For important recent review of palladium- and nickel-mediated aryl aminations, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067. (d) Hartwig, J. F. *Synlett* **1997**, 329−340. (e) Yang, B. H.; Buckwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

(3) For representative examples dealing with the amination of aryl chlorides, see: (a) Wolfe, J. P.; Buckwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413−2416. (b) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinburg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840−1853. (c) Bei, X.; Guram, A. S.; Turner, H. W.; Weinburg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237−1240. (d) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (f) Brenner, E.; Fort, Y. *Tetrahedron Lett.* **1998**, *39*, 5359−5362. (g) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (h) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (i) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301−309. (j) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810.

(4) For more examples dealing with couplings involving aryl chlorides, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2411−2413. (b) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3387−3388. (c) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 481−483. (d) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (e) Bei, X.; Guram, A. S.; Turner, H. W.; Weinburg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (f) Indolese, A. F. *Tetrahedron Lett* **1997**, *38*, 3513−3516. (g) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030. (h) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993−2996.

(5) (a) Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725−728. (b) Arduengo, A. J. III; Krafczyk, R. *Chem. Zeit.* **1998**, *32*, 6−14. (c) Herrmann, W. A.; Köcher, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2163−2187.

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mediated olefin metathesis[7,8] has opened new opportunities in catalysis.

Recently, we examined the thermochemistry of transition metal-centered ligand substitution involving nucleophilic *N*-heterocyclic carbenes.[8] This allowed us to quantify the considerable stabilizing effect brought by this class of ligands to organometallic systems. An understanding of ligand stereoelectronic effects provided by the thermochemical investigations has led to the use of this ligand class in a ring-opening/closing metathesis system.[8a]

We have most recently focused our efforts on palladium-mediated processes which appear to benefit from the use of sterically demanding, electron-donating ligands. We have recently reported on the Suzuki and Kumada cross-coupling reactions of aryl chlorides employing $Pd_2(dba)_3$ or $Pd(OAc)_2$ and an imidazolium salt as catalyst systems.[13,14] The use of aryl chlorides in coupling chemistry has proven difficult but would economically benefit a number of industrial processes.[15,16]

Considering the major effect of the use of bulky carbene ligands in the related C−C bond formation processes discussed above, we wondered if catalytic amination could be performed with the help of a judiciously selected bulky imidazolium salt. We now wish to report the palladium-mediated C−N bond coupling of normally less reactive aryl chlorides with various amines using a bulky nucleophilic carbene as supporting ligand.[17]

On the basis of our recent success with IMesHCl[18] (**3**, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and IPrHCl[19] (**4**, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as ancillary ligand precursors in Suzuki[13] and Kumada[14] couplings involving aryl chlorides, a similar protocol was used to perform the amination of aryl chlorides. In an effort to select the most effective imidazolium salt, a number of 1,3-aryl-substituted imidazolium chlorides (Scheme 1, **1**−**4**) were used in a model reaction (Table 1).

Scheme 1. Imidazolium Salts

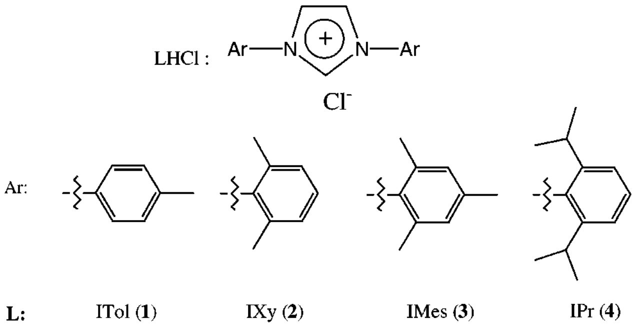
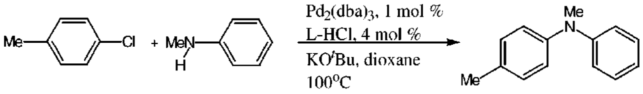


Table 1. Amination of 4-Chlorotoluene Using Different Imidazolium Chlorides



entry	ligand L	time (h)	yields (%)[a]
1	none	3	0
2	ITol	3	<5
3	IXy	3	11
4	IMes	3	22
5	IPr	3	98

[a] Isolated yields represent the average of two runs.

The bulky (vide infra) IPrHCl (**4**) was found to be the most effective imidazolium salt examined, leading to isolation of the coupled product in a 98% isolated yield (Table 1, entry 5).

A survey of catalytic cross-coupling of aryl halides with primary and secondary cyclic or acyclic amines using IPrHCl (**4**) as the supporting ligand is provided in Table 2. The role of the added base KO^tBu is 2-fold: it initially deprotonates the imidazolium chloride to form the free carbene ligand in situ which then coordinates to Pd(0). It also serves as a strong base to neutralize the HX formed in the course of the coupling reaction. This catalytic system proved to be general and efficient as shown by results presented in Table 2.

The less reactive unactivated aryl chlorides reacted with various amines including primary (Table 2, entries 6, 7, and 9) and secondary cyclic (Table 2, entries 1−3 and 10) or acyclic (Table 2, entries 4, 5, and 11) amines in high yields. Ortho-substitued aryl chlorides reacted with amine without difficulty. The reaction of 4-chlorotoluene with highly hindered amines (Table 2, entry 7) leads to lower yields.

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(6) Applications of phosphine ligands in homogeneous catalysis: (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles andApplications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (b) Parshall, G. W.; Ittel, S. *Homogeneous Catalysis*; J. Wiley and Sons, New York, 1992. (c) Pignolet, L. H., Ed. *Homogeneous Catalysis with Metal Phosphine Complexes*; Plenum: New York, 1983.

(7) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2490−2493. (b) Scholl, M.; Trnka, T. M.; Morgan, J. T.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250.

(8) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. (b) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370−2375.

(9) Voges, M. H.; Rømming, C.; Tilset, M. *Organometallics* **1999**, *18*, 529−533.

(10) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96.

(11) (a) Herrmann, W. A.; Elison, M.; Fisher, J.; Köcher, C.; Autus, G. R. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371−2373. (b) Herrmann, W. A.; Fischer, J.; Elison, M.; Köcher, C.; Autus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 772−780. (c) McGuinness, D. S.; Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165−178.

(12) Herrmann, W. A.; Goossen, L. T.; Köcher, C.; Autus, G. R. J. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 2805−2807.

(13) (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (b) Huang, J.; Grasa, G.; Zhang, C.; Trudell, M. L.; Nolan, S. P. Manuscript in preparation.

(14) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* In press.

(15) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Cornils, B., Herrmann, W. A., Eds. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996.

(16) (a) *Chem. Eng. News* **1998**, June 1, 24. (b) *Chem. Eng. News* **1998**, July 13, 71.

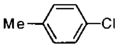
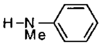
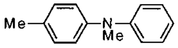
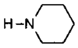
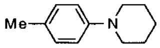
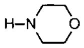
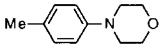
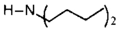
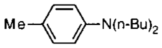
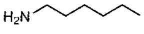
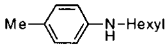
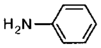
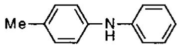
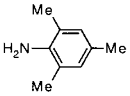
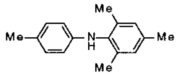
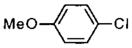
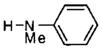
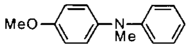
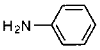
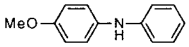
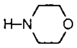
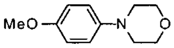
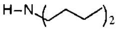
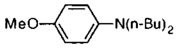
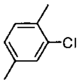
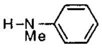
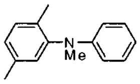
(17) A recent report by Hartwig shows that a bulky monodentate tertiary phosphine can be used as ancillary ligand in aryl amination: Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

(18) (a) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534. (b) Arduengo, A. J., III; Dias, H. V. R.; Calabrese, J. C.; Davidson, F. J. *J. Am. Chem. Soc.* **1992**, *114*, 4391−4393.

(19) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. Manuscript in preparation.

Table 2. Amination of Aryl Chlorides with Various Amines[a]

$$\mathrm{ArCl} + \mathrm{HNR'R''} \xrightarrow[\mathrm{KO^tBu,\ dioxane}]{\mathrm{Pd_2(dba)_3,\ IPrHCl}} \mathrm{Ar\text{-}NR'R''}$$

entry	Ar-Cl	HNR'R"	Ar-NR'R"	yield (%)[b]
1				99
2				96
3				82
4				95
5				86[c]
6				96
7				59
8				91
9				91
10				80
11				98
12				94

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of amine, 1.5 mmol of KO*t*Bu. 1.0 mol % of $Pd_2(dba)_3$, 4.0% IPrHCl (2 L/Pd), 3 mL of dioxane, 100 °C. Reactions were complete in 3−30 h, and reaction times were not minimized. [b] Average isolated yields of two runs. [c] Dialkylaniline was isolated as a byproduct in 5% yield.

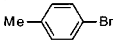
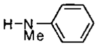
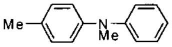
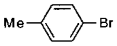
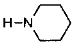
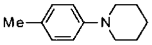
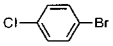
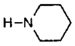
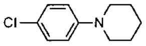
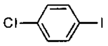
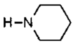
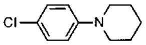
The generality of the method is illustrated by the efficient coupling of unhindered aryl chlorides with both acyclic primary and secondary alkylamines. To the best of our knowledge, no reported catalyst allows this transformation.

Generally, aminations involving aryl bromides and iodides proceed under milder conditions than those involving aryl chlorides. To examine the halide substituent effect, the efficiency and selectivity of the present catalytic system for amination of aryl bromides and iodides was examined. Both aryl bromides and iodides (Table 3) reacted with amines smoothly at room temperature. Most interesting in these studies involving an aryl bearing both chloro and iodo (or bromo) substituents is the observation that bromo and iodo functionalities can be converted at room temperature (Table 3, entries 3 and 4) and the remaining chloro functionality can subsequently be converted at more elevated temperatures. This could prove to be a significant advantage in process chemistry.

While the detailed mechanism remains to be elucidated, it seems apparent that arylamidopalladium intermediates are involved in this reaction as previously observed.[2,3] It appears to us that both steric and electronic effects combine to mediate the coupling process. Initially, the electron donor properties of the carbene facilitate the activation of aryl chlorides. A secondary effect may be provided by the bulk located at the ortho positions of the carbene aryl group.

Table 3. Amination of Aryl Bromides and Iodides

$$\mathrm{ArX} + \mathrm{HNR'R''} \xrightarrow[\mathrm{KO^tBu,\ dioxane}]{\mathrm{Pd_2(dba)_3,\ IPrHCl}} \mathrm{Ar\text{-}NR'R''}$$

entry	Ar-X	HNR'R"	Ar-NR'R"	yield (%)[b]
1				89
2				83
3				94
4				97

[a] Reaction conditions: 1.0 mmol of aryl halides, 1.2 mmol of amine, 1.5 mmol of KO*t*Bu. 1.0 mol % of $Pd_2(dba)_3$, 4.0% IPrHCl (2 L/Pd), 3 mL of dioxane, room temperature. Reactions were complete in 3−30 h, and reaction times were not minimized. [b] Average isolated yields of two runs.

Results of structural studies in related platinum complexes of general formulation L_2PtMe_2 (L= nucleophilic carbene) indicate that these ortho positions are oriented directly toward the groups involved in the reductive elimination step. Steric hindrance imparted by the ligands may therefore favor this reductive elimination step. We believe a combination of effects are at play: once the electron donor carbene imparts enough electron density to the metal to enable it to perform the oxidative addition, the ligand sterics may subsequently facilitate the reductive elimination. The steric effects provided by ortho substituents on the carbene aryl groups influence the efficiency of the catalytic transformation in a dramatic fashion (Table 1). Our thermochemistry studies on ruthenium systems involving these carbenes[8b,19] show that ITol is the best electron donor (ITol > IMes ≈ IXy > IPr) while IPr is the most bulky ligand (IPr > IMes ≈ IXy > ITol). Up to now the catalytic activity of systems involving these various imidazolium salts follows the steric trend.

In summary, a general and efficient methodology for the amination of aryl chlorides (and bromides and iodides) has been developed. The simple methodology makes use of a combination of a palladium(0) complex and an imidazolium chloride forming the catalytic precursor which proves effective for unactivated aryl chlorides as well as aryl bromides and iodides in high isolated yields. This methodology provides the first report of aryl amination involving aryl chlorides with both acyclic primary and secondary alkylamines. Application of similar and improved protocols[20] to related coupling reactions using nucleophilic carbene as supporting ligand is ongoing.

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Supporting Information Available: Experimental procedures and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) We have recently determined that 1 equiv of the IPr•HCl salt could be used instead of two, leading to similar isolated yields in approximately half the time. A full report of this improvement is forthcoming.