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Improved Carbonylation of Heterocyclic Chlorides and Electronically Challenging Aryl Bromides

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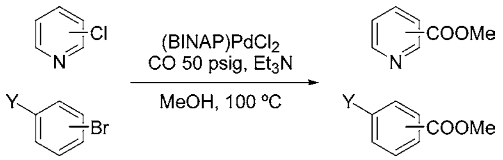
ABSTRACT



Optimized conditions are described that effect the carbonylation of diverse heterocyclic chlorides to yield the desired alkyl esters. In addition, bromoanilines and bromoanisoles, which normally are poor substrates under standard carbonylation protocols, were efficiently converted to the desired products under these new conditions. The nature of the metal bidentate ligand complex was found to be critical. Specifically, a correlation between ligand bite angle and catalytic efficiency is documented.

The quest to activate aryl chloride bonds catalytically has resulted in notable advances over the past decade.[1] The metal-catalyzed carbonylation of aryl chlorides is of particular interest, as it provides synthetically useful carbonyl derivatives.[2] In addition, the aromatic chlorides are typically less expensive and often more readily available compared to the corresponding aromatic bromo, iodo, and triflate derivatives.

Metal catalysts employing bidentate ligands as part of their coordination complex have been used successfully by both the Milstein and Beller groups in the carbonylation of chlorobenzene.[3] Milstein et al.[3a] utilized a bis(diisopropyl phosphino)propane (dippp) palladium complex, whereas Beller et al. employed a palladium catalyst generated from one of the commercially available Josiphos ligands.[3b−e] Although these findings represent a significant advance in the field and effect excellent carbonylation reactions of simple aryl chlorides, they both have drawbacks. The dippp ligand is currently not commercially available and can be difficult to prepare, whereas the Josiphos ligands must be used in large excess relative to the metal in order to keep the palladium in solution. We recently required an efficient

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(1) (a) Littke, A.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Littke, A.; Schwarz, L.; Fu, G. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348. (c) Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (d) Littke, A.; Fu, G. *J. Org. Chem*. **1999**, *64*, 10−11. (e) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555−1557. (f) Koike, T.; Mori, A. *Synlett* **2003**, *12*, 1850−1852. (g) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem*. **2003**, *68*, 8416−8423. (h) Bedford, R. B.; Cazin, C. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987−999. (i) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746−4748. (j) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761−3764. (k) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031−3033. (l) Remmele, H.; Koellhofer, A.; Plenio, H. *Organometallics* **2003**, *22*, 4098−4103. (m) Spielvogel, D. J.; Davis, W. M.; Buchwald, S. L. *Organometallics* **2002**, *21*, 3833−3836. (n) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127−14136.

(2) (a) Blaser, H.-U.; Diggelmann, M.; Meier, H.; Naud, F.; Scheppach, E.; Schnyder, A.; Studer, M. *J. Org. Chem.* **2003**, *68*, 3725−3728. (b) Hayashi, T.; Tang, J.; Kato, K. *Org. Lett.* **1999**, *1*, 1487−1489. (c) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1996**, *61*, 7482−7485. (d) Takeuchi, R.; Suzuki, K.; Sato, N. *J. Mol. Catal*. **1991**, *66*, 277−288. (e) Dufaud, V.; Thivolle-Cazat, J.; Basset, J.-M. *J. Chem. Soc., Chem. Commun.* **1990**, 426−427. (f) Crettaz, R.; Wasser, J.; Bessard, Y. *Org. Process Res. Dev.* **2001**, *5*, 572−574.

(3) (a) Yehoshua, B.-D.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742−8744. (b) Magerlein, W.; Indolese, A. F.; Beller, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2856−2859. (c) Beller, M.; Magerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, 1098−1109. (d) *J. Organomet. Chem.* **2002**, *641*, 30−40. (e) Beller, M.; Zapf, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, NJ, 2002. (f) Beller, M.; Magerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, *7*, 1098−1109.

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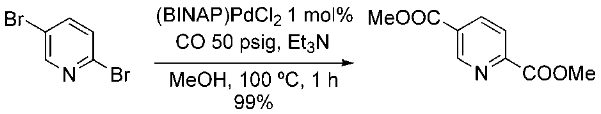
carbonylation of a halo-pyridine that would be practical and amenable for large-scale synthesis. In this manuscript, we disclose our findings in this regard and specifically document a correlation between catalyst activity and bidentate ligand bite angle.

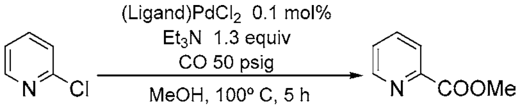
We initiated a catalyst screening for the carbonylation of halo-pyridines and noted an exceptional rate enhancement with the use of the catalyst (*rac*-BINAP)PdCl$_2$ in comparison to palladium catalysts containing monodentate ligands. For example, 2,5-dibromopyridine was dicarbonylated with (*rac*-BINAP)PdCl$_2$ to produce dimethyl-2,5-dicarboxypyridine in 99% yield and in only 1 h (Scheme 1).

Scheme 1



Further screening of catalyst systems containing bidentate ligands revealed an interesting trend (Table 1). The rate of conversion was markedly dependent upon the bite angle of the ligand. The most active catalysts were those containing bidentate phosphine ligands with a natural bite angle near 90°, with the one exception of Xantphos (110°).[4] The optimal ligands for carbonylation of 2-chloropyridine in methanol under relatively low CO pressure conditions were *rac*-BINAP, tol-BINAP, dppp, and Xantphos.

Table 1. Effect of Bite Angle on Conversion of 2-Chloropyridine[5]

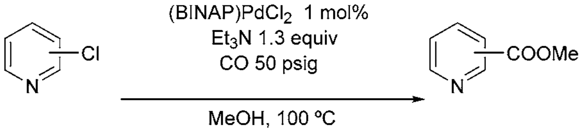


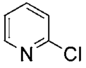
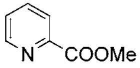
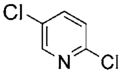
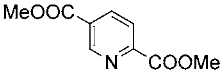
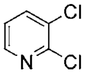
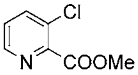
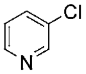
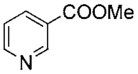
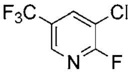
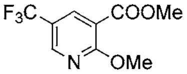
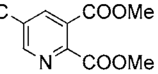
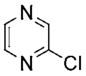
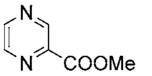
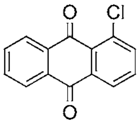
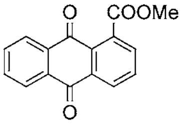
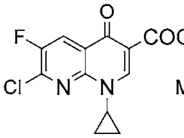
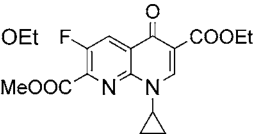
ligand	n(deg)	%conversion
dppm	72	3
dppe	78	6
dppp	91	86
tol-BINAP	91	98
BINAP	92	94
dppb	99	35
DPEphos	102	13
PHANEPHOS	104	13
Xantphos	110	99
NORPHOS	123	1

(*rac*)-BINAP is readily available, air-stable, and one of the least expensive bidentate ligands. We decided to explore the capabilities of (BINAP)PdCl$_2$ as a carbonylation catalyst for more challenging substrates: aromatic chlorides and electron-rich aromatic bromides.

Carbonylation of 2,5-dichloropyridine with 1 mol % (BINAP)PdCl$_2$ at 50 psig of CO pressure and 100 °C with triethylamine (2 equiv) in methanol resulted in smooth transformation to the dimethyl 2,5-dicarboxypyridine in 8 h (Table 2, entry 2). There was no evidence of palladium black deposition during the course of the reaction, which indicates the excellent stability of this catalyst system, and no reduced pyridine products were noted.

Table 2. Carbonylation of Heterocyclic Chlorides



entry	heteroaryl chloride	product	time (h)	yield (%)
1			5	99
2			8	98
3			48	86
4			24	0
5[a]			14	60
		+ 		10
6			4	99
7			18	61
8			16	63

[a] 3 mol% catalyst used.

Methanol was an adequate solvent; it was not necessary to use the more CO-solubilizing solvent *n*-butanol.[6] Attempts to extend the scope of these conditions to chlorobenzene with (BINAP)PdCl$_2$ failed; however, other heterocyclic substrates underwent good conversion to provide the desired ester products. The carbonylation of 2,3-dichloropyridine (entry

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(4) Xantphos has been shown capable of both *cis* and *trans* coordination modes. See: Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043−6048. (b) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895−904.

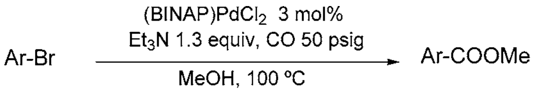
(5) For a definition of natural bite angle see: Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299−304.

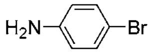
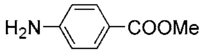
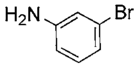
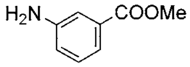
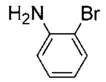
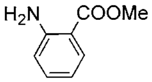
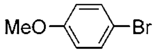
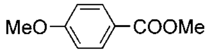
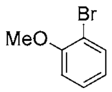
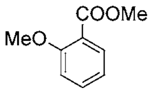
(6) For a comparative study of solubility of CO in alcohols, see: Tonner, S. P.; Wainwright, M. S.; Trimm, D. L. *J. Chem. Eng. Data* **1983**, *28*, 59−61.

3) was notably slower than that of 2,5-dichloropyridine (entry 2). 3-Chloropyridine is an exception (entry 4), as it was inert under our conditions. Reaction of 2-fluoro-3-chloro-5-trifluoromethylpyridine (entry 5) returned two products. The major product was the expected 3-carboxypyridine compound. The minor product, surprisingly, was the 2,3-dicarboxypyridine compound. The minor product is not formed from the major, as resubjecting the major product to the carbonylation conditions did not generate the minor product. It is likely that a chloride ion in the reaction solution displaced the fluoride at the 2-position of the pyridine ring, followed by carbonylation at that position.

Carbonylation of bromoaniline substrates is difficult and is usually accomplished by amine protection to modulate the electron density of the aniline ring.[7] Employing the mild (BINAP)PdCl$_2$ conditions, both *o*-bromoaniline and *m*-bromoaniline were smoothly transformed to the corresponding esters in excellent yields overnight (Table 3). The conversion of *p*-bromoaniline was more sluggish and only 50% complete at 48 h. Bromoanisoles were also cleanly carbonylated to produce methoxybenzoic esters in excellent yields. *o*-Bromoanisole and *p*-bromoanisole both performed equally well under these mild conditions.

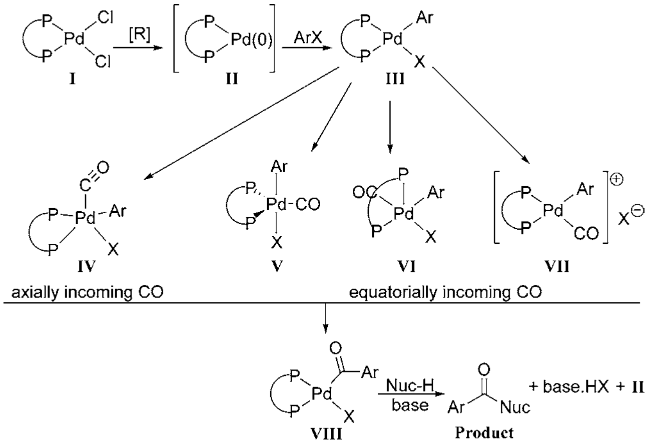
Table 3. Carbonylation of Bromoanilines and Bromoanisoles



entry	aryl bromide	product	time (h)	yield (%)
1			48	50
2			16	98
3			16	92
4			16	96
5			16	99

The mechanism of palladium-catalyzed carbonylation reactions employing monodentate ligands has been investigated by several groups.[8] The mechanism often invoked requires a dissociation of one of the phosphine ligands to provide the coordinatively unsaturated metal complex followed by ligation to carbon monoxide, followed by migration of the aryl group and subsequent generation of the acyl palladium complex. The acyl complex then reacts with a nucleophile such as an alcohol or amine to give ester or amide products.[9] Although the mechanism involving a palladium catalyst containing a rigid bisphosphine bidentate ligand could occur similarly, it would be less entropically favored for one of the phosphines to dissociate completely.[10] This suggests that the carbonylation involving the bisphosphine ligands may proceed via an alternate mechanism. A few possible pathways are outlined below and summarized in Scheme 2.

Scheme 2



As in the standard mechanism, the process is initiated with reduction of **I** to produce a reactive Pd(0) complex **II**, which oxidatively adds to the Ar−X bond to generate complex **III** (Scheme 2). At this point, CO may interact with **III** either axially or equatorially. The axial approach to **III** leads to a five-coordinate complex **IV**, reminiscent of the interaction between CO and Vaska's complex.[11] The ~90° ligand bite angle is optimized for the square pyramidal geometry of **IV**. Aryl migration to CO restores the square planar geometry as the acyl complex.

The equatorial approach requires some reorganization of ligands around the metal center, resulting in complexes of the general type **V**, **VI**, and **VII**.

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[7] Mahmud, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2001**, *57*, 4095−4105. (b) Lovely, C. J.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079−2082. (c) Torisawa, Y.; Nishi, T.; Minamikawa, J.-I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2493−2495. (d) Lapidus, A. L.; Petrovskii, K. B.; Bruk, L. G.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1999**, *35*, 1636−1639. (e) Yun, W.; Li, S.; Wang, B.; Chen, L. *Tetrahedron Lett.* **2001**, *42*, 175−177. (f) Cai, M.-Z.; Song, C.-S.; Huang, X. *Synth. Commun.* **1997**, *27*, 361−366. (g) Devi, R.; Pardhasaradhi, M.; Iyengar, D. S. *Tetrahedron* **1994**, *50*, 2543−2550. (h) Davies, S. G.; Goodwin, C. J.; Pyatt, D.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1413−1420.

[8] (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318−3326. (b) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 532−534. (c) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115−4127. (d) Moser, W. R.; Wang, A. W.; Kjeldahl, N. K. *J. Am. Chem. Soc.* **1988**, *110*, 2816−2820.

[9] (a) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428−434. (b) Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, *6*, 1640−1651. (c) Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466−3478. (d) van Leeuwen, P. W. N. M.; Zuideveld, M. A.; Swennenhuis, B. H. G.; Freixa, Z.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; Lutz, M.; Spek, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 5523−5539.

[10] (a) One example of monodentate coordination of BINAP has been reported for an osmium cluster: Prestopino, F.; Persson, R.; Monari, M.; Focci, N.; Nordlander, E. *Inorg. Chem. Commun.* **1998**, 302−304. (b) For an example of carbonylation of neutral palladium complexes containing hemi-labile bidentate ligands, see: Frankcombe, K.; Cavell, K.; Knott, R.; Yates, B. *Chem. Commun.* **1996**, 781−782.

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Trigonal bipyramidal complexes of Pd and Pt have been described and have been postulated as intermediates in reaction pathways.[12] The coordinatively saturated intermediate **V** offers several advantages. For d^8 metals, electron density is greater in the *xy* plane than along the *z* axis in the trigonal pyramidal geometry, and so bond formation should be favored in the equatorial plane with back-bonding ligands such as CO. To accommodate the incoming equatorial CO ligand, the σ-donating Ar and X groups are both pushed out of the plane. The axial σ-donating Ar and X ligands may exert a stabilizing influence on the trigonal pyramidal Pd(II) complex. The lability of the axial Ar group makes migration facile. The preference for equatorial ligation of good back-bonding ethylene ligands and the stabilizing influence of the axial Ar group is precedented for trigonal bipyramidal complexes (analogous to **V**) arising from the analogous square planar Pd(II) and Pt(II) complexes containing chelating ligands with small bite angles.[13]

Complex **VI** arises from one of the phosphines of the bidentate ligand moving into the axial position as CO approaches. Here clearly, a ~90° bite angle could stabilize the intermediate. However, in complexes of type **VI**, the CO group may not necessarily come in *cis* to the Ar group as drawn in Scheme 2. A *trans* arrangement would require reorganization to enable migration and acyl complex formation. Complexes **IV**, **V**, and **VII** enforce the requisite *cis* geometry. Complex **VI** may not be a productive intermediate for the carbonylation reaction with bidentate ligands.

The cationic complex **VII** maintains the preferred square planar geometry. Presumably **VII** is formed through a five-coordinate intermediate where CO replaces the X group. Although cationic Pd(II) complexes have been shown to be very active catalysts for polymerization reactions of CO with ethylene, preliminary experiments show minimal effects due to changes of the counterion. After migration, an open coordination site is filled by the returning X, which reconstitutes the square planar geometry. Studies are underway to determine which pathway(s) is operative for our system.

In conclusion, we have developed the use of (BINAP)-$PdCl_2$ as an air-stable and robust carbonylation catalyst for various heteroaromatic chlorides, as well as for electronically challenging bromides. (BINAP)$PdCl_2$ is simple to prepare, relatively inexpensive, and stable to air. The conditions for carbonylation are relatively mild (50 psig CO, 100 °C, and a slight excess of tertiary amine base) and provide products in good to excellent yields. (BINAP)$PdCl_2$ is a practical and economical alternative for the carbonylation of several heterocyclic chlorides and aromatic bromides. We are currently engaged in studies to elucidate the mechanism of the carbonylation and identity of the active intermediates.

Supporting Information Available: Experimental details and characterization data details. This material is available free of charge via the Internet at http://pubs.acs.org.

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