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Palladium-Catalyzed Cross-Coupling of Pyrrole Anions with Aryl Chlorides, Bromides, and Iodides

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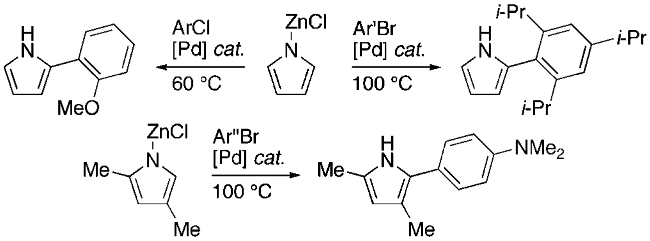
ABSTRACT



A general method for the conversion of pyrrole anions to 2-arylpyrroles has been developed. Using a palladium precatalyst and sterically demanding 2-(dialkylphosphino)biphenyl ligands, (pyrrolyl)zinc chloride may be cross-coupled with a wide range of aryl halides, including aryl chlorides and aryl bromides, at low catalyst loadings and under mild conditions. A high degree of steric hindrance is tolerated. Certain ring-substituted pyrrole anions have also been arylated with aryl bromide substrates.

In the pursuit of new low-coordinate complexes of late transition metals, we became interested in pyrrole-derived chelate ligands[1] and in the incorporation of sterically demanding aryl groups in the positions flanking the nitrogen atoms. In several cases of interest, the precursor 2-arylpyrroles had not been reported.[2,3] Because 2-arylpyrroles are also of interest in the synthesis of fluorescent dyes,[4a] pharmaceuticals,[4b] and insecticides,[4c] a general method for the arylation of pyrroles could be widely useful.

The great versatility of Pd-catalyzed cross-coupling in C−C bond formation includes some noteworthy routes to 2-arylpyrroles. Polysubstituted pyrroles have been prepared by elegant multicomponent coupling reactions;[5] less substituted 2-arylpyrroles have been obtained by Suzuki cross-coupling of *N*-protected pyrrole derivatives.[6,7] The pyrrole anion, as its (chloro)zinc derivative, couples with iodoben-

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(1) Selected recent examples: (a) Halper, S. R.; Cohen, S. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2385−2388. (b) Gao, G.; Korobkov, I.; Gambarotta, S. *Inorg. Chem.* **2004**, *43*, 1108−1115. (c) Love, J. B.; Salyer, P. A.; Bailey, A. S.; Wilson, C.; Blake, A. J.; Davies, E. S.; Evans, D. J. *Chem. Commun.* **2003**, 1390−1391. (d) Li, Y.; Turnas, A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2002**, *41*, 6298−6306. (e) Chen, Q.; Dolphin, D. *Can. J. Chem.* **2002**, *80*, 1668−1675.

(2) Methods for 2-arylpyrrole synthesis include: (a) Guizzardi, B.; Mella, M.; Fagnoni, M.; Albini, A. *Tetrahedron* **2000**, *56*, 9383−9389. (b) Trofimov, B. A.; Mikhaleva, A. I.; Vasil'tsov, A. M.; Schmidt, E. Y.; Tarasova, O. A.; Morozova, L. V.; Sobenina, L. N.; Preiss, T.; Henkelmann, J. *Synthesis* **2000**, 1125−1132. (c) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031−5041. (d) Katritzky, A. R.; Li, J.; Gordeev, M. F. *Synthesis* **1994**, 93−96. (e) Oda, K.; Machida, M. *J. Chem. Soc., Chem. Commun.* **1993**, 437−438. (f) Ohkura, K.-i.; Seki, K.; Terashima, M.; Kanaoka, Y. *Heterocycles* **1990**, *30*, 957−962. (g) Kruse, C. G.; Bouw, J. P.; Van Hes, R.; Van de Kuilen, A.; Den Hartog, J. A. J. *Heterocycles* **1987**, *26*, 3141−3151. (h) Buhr, G. *Chem. Ber.* **1973**, *106*, 3544−3558. (i) Rapoport, H.; Look, M. *J. Am. Chem. Soc.* **1953**, *75*, 4605−4607. See also refs 4−8.

(3) Our attempt to synthesize 2-mesitylpyrrole, for example, by adaptation of an existing route (ref 2g) afforded the desired compound in 1% yield. More heavily substituted 2-mesitylpyrroles have been obtained indirectly from azidocyclobutenes; see ref 2h.

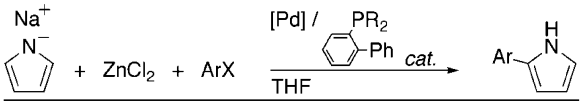
(4) Selected references: (a) Burghart, A.; Thoresen, L. H.; Chen, J.; Burgess, K.; Bergström, F.; Johansson, L. B.-Å. *Chem. Commun.* **2000**, 2203−2204. (b) Pinna, G. A.; Loriga, G.; Murineddu, G.; Grella, G.; Mura, M.; Vargiu, L.; Murgioni, C.; La Colla, P. *Chem. Pharm. Bull.* **2001**, *49*, 1406−1411. (c) Hunt, D. A. *Pest. Sci.* **1996**, *47*, 201−202.

(5) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468−469.

(6) (a) Knight, L. W.; Huffman, J. W.; Isherwood, M. L. *Synlett* **2003**, 1993−1996. (b) Thoresen, L. H.; Kim, H.; Welch, M. B.; Burghart, A.; Burgess, K. *Synlett* **1998**, 1276−1278. (c) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025−1027.

10.1021/ol048367m CCC: $27.50

Table 1. Pd-Catalyzed Arylation of (Pyrrolyl)zinc Chlorides[a]



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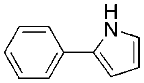
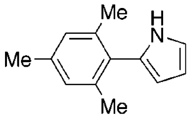
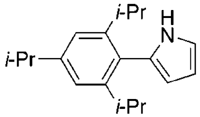
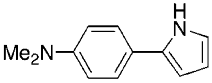
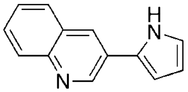
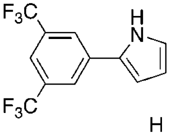
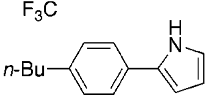
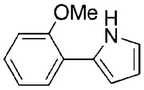
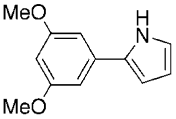
1[b]	I	100 °C		90
2[b,c]	Br	100 °C		90
3[d,e]	Br	100 °C		70
4	Br	100 °C		48
5[f]	Br	100 °C		70
6[b,e]	Br	80 °C		90
7	Cl	60 °C		71
8[b]	Cl	60 °C		93
9	Cl	60 °C		81

[a] Unless noted otherwise: 1.0 equiv of ArX, 1.0 M in THF; 1.6 equiv of [Na$^+$ ($C_4H_4N^-$)]/$ZnCl_2$; 0.5 mol % $Pd(OAc)_2$ and ligand (R = *t*-Bu); 16−25 h. [b] With 3.0 equiv of [Na$^+$ ($C_4H_4N^-$)]/$ZnCl_2$. [c] With 8.2 mmol of ArBr in 20 mL of THF and 0.25 mol % $Pd_2(dba)_3$; 44 h. [d] With 2.0 mol % $Pd_2(dba)_3$, 4.0 mol % phosphine, and 4.0 equiv of [Na$^+$ ($C_4H_4N^-$)]/$ZnCl_2$; 41 h. [e] Ligand with R = cyclohexyl was used. [f] When R = Cy, reaction at 60 °C for 16 h gave 72% yield of *N*-arylpyrrole.

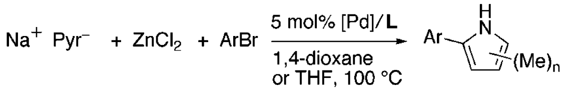
zene at relatively high temperatures and catalyst loadings, giving a 4:1 mixture of 2- and 3-phenylpyrrole in moderate yield.[8] This method served as our starting point. An impressively versatile and convenient method for the catalytic C-arylation of free azoles, reported subsequently, works well for the reaction of pyrrole itself with iodobenzene.[9]

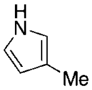
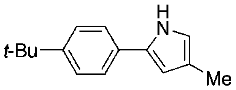
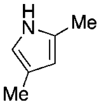
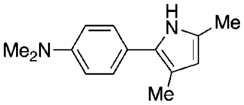
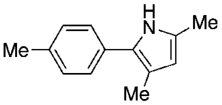
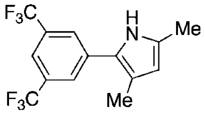
Despite these important advances, a general protocol for the 2-arylation of *N*-deprotonated pyrroles under mild conditions had not been reported. We report here that sterically demanding, electron-rich dialkylphosphinobiphenyl ligands,[10] developed by Buchwald and co-workers, support the Pd-catalyzed 2-arylation of pyrrolylzinc chloride with a variety of aryl halide substrates, including aryl chlorides and very sterically hindered bromides. These reactions require far lower temperatures and, in most cases, catalyst loadings than the pyrrole arylations reported to date. This method also allows the coupling of certain ring-substituted pyrrolyl anions with aryl bromides.

The results for the arylation of pyrrolylzinc chloride, generated in situ from pyrrolylsodium and zinc chloride,[11] are summarized in Table 1. These reactions proceed with generally high (≥19:1) selectivity for the 2-aryl isomer over the easily separated 3-isomer. Aryl chloride substrates (entries 7−9), interestingly, react at a lower temperature than do iodobenzene (entry 1) or aryl bromides. Both electron-rich (entry 4)[12] and electron-poor (Entry 6) aryl bromide substrates may be used. A high degree of steric hindrance is tolerated, as illustrated by the use of aryl bromides bearing methyl or isopropyl groups in both *ortho* positions (entries 2 and 3), although in the latter case a higher catalyst loading (4 mol % Pd) is required. In the case of the heterocyclic substrate 3-bromoquinoline (entry 5), either 2-arylation or *N*-arylation may be achieved efficiently, depending on the supporting ligand used.[13]

The *N*-(chlorozinc) derivatives of certain ring-substituted pyrroles, bearing methyl (Table 2) or aryl (Table 3) groups, may also be arylated by this method. Both electron-rich and electron-poor aryl bromides are effective coupling partners in these reactions.[14,15] Compared to similar reactions of the parent pyrrolylzinc chloride, higher catalyst loadings (5

Table 2. Pd-Catalyzed Arylation of *C*-Methylated Pyrrole Anions



entry	Pyr–H	rxn time	product	yield (%)
1[a,e]		43h		64
2[b,d,e]		17h		78
3[c,d,f]		37h		64
4[b,d,g]		54h		75

[a] 0.5 M ArBr in THF; 1.6 equiv of [Na$^+$ Pyr$^-$]/$ZnCl_2$; with 2.5 mol % $Pd_2(dba)_3$. [b] 0.4 M ArBr in THF. [c] 1.3 M ArBr in 1,4-dioxane. [d] With $Pd(OAc)_2$; 2.0 equiv of [Na$^+$ Pyr$^-$]/$ZnCl_2$. [e] **L** = 2-(di-*tert*-butylphosphino)biphenyl. [f] **L** = 2-(dicyclohexylphosphino)biphenyl. [g] **L** = 2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl.

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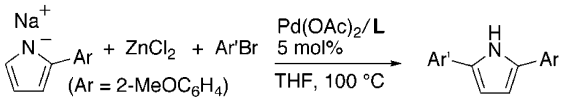
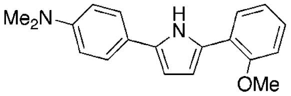
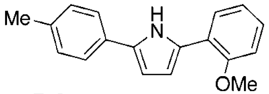
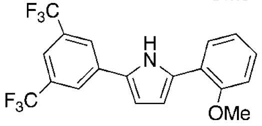
(7) Negishi coupling of (1-dimethylaminopyrrol-2-yl)zinc chloride, prepared indirectly via directed lithiation, with C_6H_5Br and 1,4-$Br_2C_6H_4$ has also been reported: Soloducho, J. *Synth. Met.* **1999**, *99*, 181−189.

(8) Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 1755−1758.

(9) Bromobenzene was also reported to react, albeit in lower yield: Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274−5275.

Table 3. Synthesis of 5-Aryl-2-(2′-methoxyphenyl)pyrroles[a]



entry	rxn time	product	yield (%)
1[a,c]	17h		82
2[a,d]	24h		83
3[b,e]	54h		92

[a] [ArBr] = 0.34 M; 1.5 equiv of [Na$^+$ Pyr$^-$]/ZnCl$_2$. [b] [ArBr] = 0.5 M; 2.0 equiv of [Na$^+$ Pyr$^-$]/ZnCl$_2$. [c] **L** = 2-(di-*tert*-butylphosphino)biphenyl. [d] **L** = 2-(di-*tert*-butylphosphino)-2′-dimethylaminobiphenyl. [e] **L** = 2-(dicyclohexylphosphino)biphenyl.

mol % Pd) are needed for efficient conversion, and further optimization will be needed before a general method is achieved. These examples, however, represent a short route to substituent patterns that would otherwise be difficult to obtain.

In summary, we have greatly expanded the scope of the palladium-catalyzed *C*-arylation of pyrrole, with a wide range of substrates including aryl chlorides and bromides, and we have demonstrated the *C*-arylation of ring-substituted pyrroles. This method affords many previously unknown 2-arylpyrroles.

Acknowledgment. We thank the MIT Department of Chemistry and UROP office for funding. We are grateful to Ms. Anna B. Folinsky for early contributions to the reaction protocol and to Professor Stephen L. Buchwald for helpful discussions.

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

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(10) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (b) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334−5341. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413−2416.

(11) Because of the air and moisture sensitivity of pyrrolyl anions, and the ready hydration of zinc chloride, these reagents were normally handled in a glovebox under nitrogen. A Schlenk-only variation, in which the pyrrole is deprotonated in situ by sodium hydride (weighed in air as its 60% dispersion in mineral oil), and the zinc chloride is added via syringe as a solution in THF, works well for some substrate combinations (Table 1, entries 4 and 6; see the Supporting Information for details). However, several other cases gave slow and/or incomplete reactions under these conditions. Further optimization will be needed to obviate in all cases the need for a glovebox.

(12) For convenience, the slightly air-sensitive product was not protected against air-oxidation during workup; the oxidation products are readily removed during the purification.

(13) The other ArX substrates gave only traces of *N*-arylpyrrole, if any. Other examples of catalytic pyrrole *N*-arylation: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (b) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481−483. (c) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827−828.

(14) One exception is 3-bromoquinoline, which under the conditions examined did not react at all with (2,4-dimethylpyrrolyl)zinc chloride.

(15) Aryl chlorides have so far given incomplete reactions. Examples include the cross-coupling of (3-methylpyrrolyl)zinc chloride with 2-chloroanisole and of [2-(2′-methoxyphenyl)pyrrolyl]zinc chloride with 1-chloro-4-*n*-butylbenzene.