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Efficient Palladium-Catalyzed *N*-Arylation of Indoles

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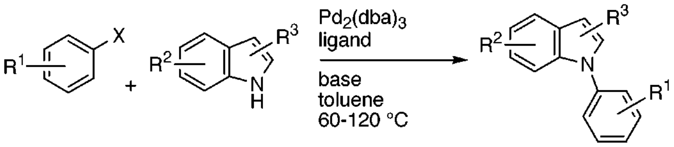
ABSTRACT



The *N*-arylation of indoles, including a variety of substituted ones, has been carried out using bulky, electron-rich phosphines as the supporting ligand in combination with $Pd_2(dba)_3$. Using this catalyst system, the efficient coupling of indole and a variety of substituted indoles with aryl iodides, bromides, chlorides, and triflates can be achieved.

The *N*-arylindole moiety is a structural element present in many biologically active and pharmaceutically important compounds. *N*-Arylindoles are of interest as angiotensin II-1 antagonists,[1] MT_1 melatonin receptor partial agonists,[2] antipsychotic agents,[3] and synthetic intermediates used in the preparation of other biologically active heterocyclic agents.[4]

Of the many methods for the synthesis of *N*-arylindoles, the Fisher indole synthesis is the best known and most widely used.[5,6] Ullmann-type coupling methodology, involving the combination of an indole with an aryl halide in the presence of base and a copper catalyst at high temperatures, is an important alternative.[7] Methods that operate under milder conditions and utilize aryl bismuth[8] and aryl lead[9] reagents have been developed. Finally, the synthesis of *N*-arylindoles may also be achieved by nucleophilic aromatic substitution in instances in which the aryl halides are activated by the presence of one or more electron-withdrawing groups.[10−12] While all of these methods are useful in its own right, each suffers from one or more limitations including a lack of generality, the use stoichiometric quantities of toxic reagents, or the need to employ harsh reaction conditions.

The palladium-catalyzed amination of aryl halides and sulfonates has been the focus of intense research in recent years, particularly from our own laboratories[13,14] and those of Hartwig[15] who first applied this methodology to the arylation of indoles using Pd/DPPF and Pd/BINAP catalyst systems.[16] Using these catalysts, Hartwig and co-workers were able to efficiently combine indole with aryl bromides that had electron-withdrawing substituents in the para position. Electronically neutral aryl bromides required the use of long reaction times and high temperatures and proceeded in moderate yield. No examples of the reactions of ortho-

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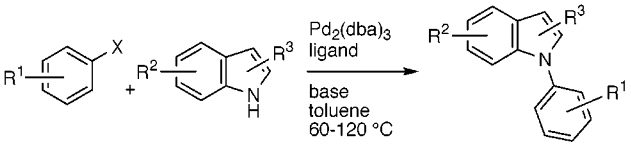
substituted aryl bromides were reported. Recently, Hartwig reported several examples of the use of the Tosoh system (Pd/P(t-Bu)$_3$) for the *N*-arylation of indoles. This protocol shortens the required reaction time for the reactions of electronically neutral aryl bromides as well as decreasing the temperature for the process to 100 °C.[17] While one example of the reaction of 3-substituted indole, skatole, with a simple ortho-substituted aryl bromide (*o*-bromotoluene) was described, reactions of similar substrates with "simple indoles" were reported to give mixtures of three products via *N*-arylation, C-arylation, and a combination of the two. No examples of reactions of polysubstituted indoles or 2- or 7-substituted indoles were reported. Herein, we describe our progress in the palladium-catalyzed *N*-arylation of indoles which overcome a number of the problems associated with the techniques described above. Of particular significance is that through the use of an appropriate set of ligands we are able to successfully couple indoles which are unsubstituted in the 3-position with ortho-substituted aryl halide and triflate substrates, and to utilize a variety of 2-, 7-, and polysubstituted indoles to provide high yields of the desired product (Scheme 1).

Scheme 1

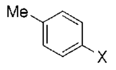
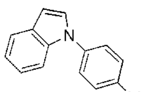
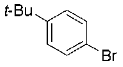
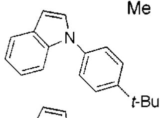
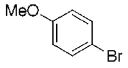
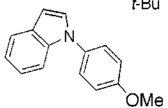
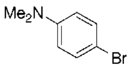
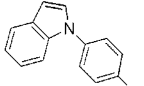
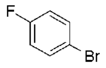
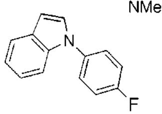
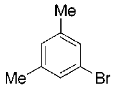
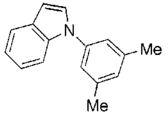
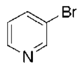
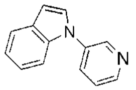
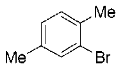
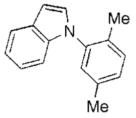
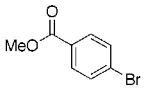
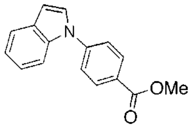
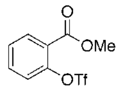
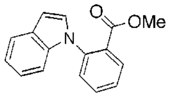
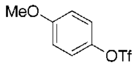
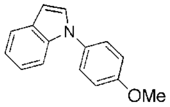
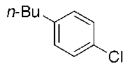
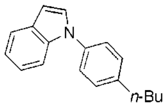
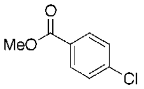
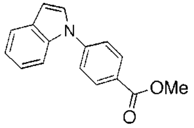


We have recently reported that the use of novel biaryl(dialkyl)phosphines as supporting ligands provides an active Pd(0) catalyst which is exceptional in the coupling of arylboronic acids (Suzuki couplings), ketone enolates, and amines with aryl bromides and chlorides.[18] The wide scope of these catalysts led us to investigate transformations involving less-reactive nitrogen nucleophiles, such as indoles (vide infra).

We were pleased to find that indole was effectively coupled with a variety of aryl chlorides, bromides, iodides, and triflates to afford the desired coupling products in good yields (Table 1). The examples of the latter are the first to be described. As previously noted above, often a mixture of three products were produced; C-arylated indoles and N,C-doubly arylated indoles were formed in addition to the desired *N*-arylindole. We found that we were able to minimize the formation of the side products by choosing an appropriate ligand (Figure 1).

Our studies showed that NaOt-Bu was the most effective base, while the use of other bases such as NaH, Et$_3$N, and Cs$_2$CO$_3$ was less successful. In the instances where the starting materials were incompatible with NaOt-Bu (including triflates), we found K$_3$PO$_4$ to be a useful alternative (Table 1, entries 12−15 and 17). Pd$_2$(dba)$_3$ was found to be the best source of palladium, while Pd(OAc)$_2$ was ineffective

Table 1. Pd-Catalyzed *N*-Arylation of Indole[a]

Entry	Aryl halide or triflate		Pd (mol %)/**L**	Product	Yield[b]
1 2 3		X=I X=Br X=Cl	2.5/**1** 2.5/**1** 2.5/**1**		90 88 87
4			1/**2**		93
5			1/**2**		84
6			1/**2**		91
7 8			5/**1** 1/**2**		77 74
9			1/**2**		87
10			3/**2**		81
11			5/**3**		87[c]
12 13			5/**1** 1/**2**		75[d] 85[d]
14			3/**3**		90[d]
15			5/**1**		87[d]
16			1/**2**		87
17			2/**2**		64[d]

a) Reaction conditions : 1.02 equiv indole, 1.0 equiv aryl halide or triflate, 1.4 equiv NaOt-Bu, 0.5–2.5 mol % Pd$_2$(dba)$_3$ (1–5 mol % Pd), 1.5–7.5 mol % ligand, toluene [0.5 M], 80–100 °C. b) Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis (average of 2 runs). c) Reaction was run at 120 °C. d) K$_3$PO$_4$ used as the base.

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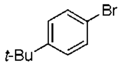
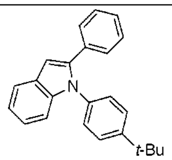
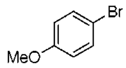
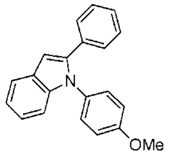
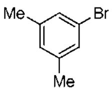
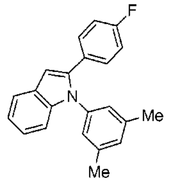
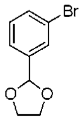
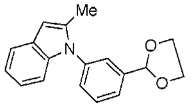
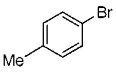
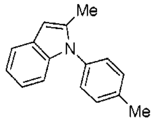
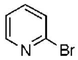
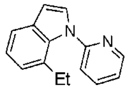
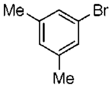
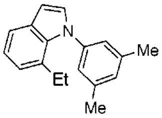
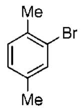
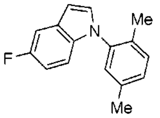
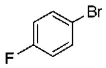
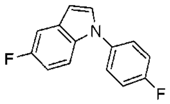
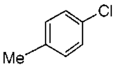
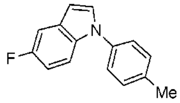
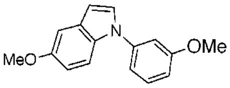
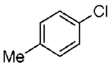
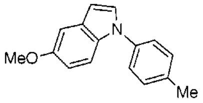
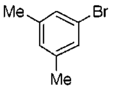
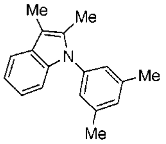
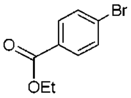
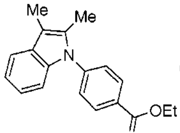
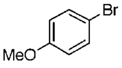
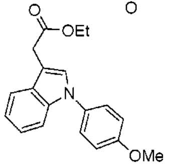
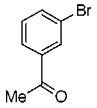
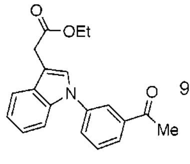
(18) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

Table 2. Coupling of Substituted Indoles with Aryl Halides and Triflates

Entry	Aryl halide	Indole Substituent	Pd (mol %)/**L**	Product	Yield^{b}
1		2-Ph	1/**4**		91
2		2-Ph	1/**4**		65
3		2-(4-fluorophenyl)	1/**4**		74
4		2-Me	3/**5**		67
5		2-Me	5/**5**		43
6		7-Et	1/**4**		94
7		7-Et	1/**4**		$53^{c,e}$
8		5-F	5/**3**		69^{f}
9		5-F	3/**2**		74^{d}
10		5-F	5/**1**		88
11		5-OMe	1/**2**		94
12		5-OMe	5/1		85
13 14		2,3-Me$_2$	1/**4** 2/**6**		95^{e} 91^{e}
15		2,3-Me$_2$	5/**6**		$60^{g,h}$
16		3-CH$_2$CO$_2$Et	1/**2**		90^{g}
17		3-CH$_2$CO$_2$Et	2/**2**		95^{g}

a) Reaction conditions : 1.02–1.08 equiv indole, 1.0 equiv aryl halide or triflate, 1.4 equiv NaO*t*-Bu, 0.5–1.5 mol % Pd$_2$(dba)$_3$ (1–3 mol % Pd), 1.5–4.5 mol % ligand, toluene [0.5 M], 80–100 °C. b) Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis (average of 2 runs). c) Reaction was run at 60 °C. d) Same as a, but with 1.2 equiv indole. e) Same as a, but with 1.12 equiv indole. f) Reaction was run at 120 °C. g) K$_3$PO$_4$ used as the base. h) Dioxane used as the solvent.

or less efficient in all cases. Toluene was found to be the optimal solvent, although in a few cases the use of dioxane was also effective. All of the reactions described herein were performed in test tubes, under argon, and all reagents were handled and weighed in the air.[19a]

Our initial work employed P,N-ligand **1**.[19b] In all of the reactions involving **1**, 2.5–5 mol % Pd is required. This restriction, combined with our experience that Pd/**1** is not effective in several cases (e.g., ortho-substituted aryl halides), prompted us to search for more reactive catalytic systems. Accordingly, several analogues of **1** were prepared and screened for reactivity in the *N*-arylation of indoles. Changing both the alkyl group on phosphorus and the 2′ aryl substituent proved beneficial. We found that the use of Pd/**2**, where the dimethylamino is replaced with an isopropyl group, and the dicyclohexylphosphine moiety is replaced with a di-*tert*-butylphosphine group, was more efficient than the Pd/**1** combination for reactions of aryl bromides and chlorides. These reactions required less catalyst and lower reaction temperatures than the parent system, while giving comparable yields. Coupling reactions of ortho-substituted aryl halides and triflates using the Pd/**1** or **2** systems, however, were

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(19) (a) The complete experimental details are available in the Supporting Information. (b) Available from Strem Chemicals, Inc.

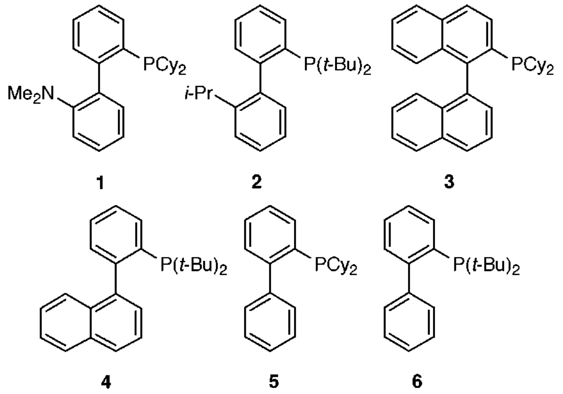

Figure 1.

sluggish. After much experimentation, we found use of **3** gave a more efficient system, although longer reaction times and more catalyst were required (Table 1, entries 11 and 14).

While the use of **2** provided a more active catalyst in combining indole with aryl chlorides and bromides, it was ineffective in the coupling reactions with aryl iodides or triflates. For aryl iodides and triflates, the use of **1** was most effective. The reactions of aryl iodides and sulfonates using the Pd/**2** system may be inefficient due to formation of bis-indolyl Pd (II) complexes.[20] A ligand such as **1**, which functions as either a monodentate or bidentate ligand, may inhibit the formation of such a species.

Given our success in the arylation of indole itself, we turned our attention to substituted indoles. We found that 3- and 5-substituted indoles show similar reactivity to indole itself and that catalysts consisting of Pd and ligands **1**−**3** were efficient (Table 2, entries 8−12, 16, and 17). In several instances issues of functional group compatibility necessitated the use of K_3PO_4 as the base.

We wished to expand the method to include a wider variety of substituted indoles. Attempts to employ catalysts based on **1**−**3** to *N*-arylate 2- or 7-substituted indoles produced a large amount of the 3-arylated and diarylated indole products. After much experimentation, a catalyst employing ligand **4** was found to be most efficient at minimizing, although not eliminating, the formation of undesired products with 2-arylindoles (Table 2, entries 1−3) and 7-alkylindoles (Table 2, entries 6 and 7). Unfortunately, conditions employing milder bases (e.g., K_3PO_4, Cs_2CO_3) were inefficient in reactions of 2-phenylindole with methyl 4-bromobenzoate. Moreover, an attempt to couple 7-ethylindole with 2-bromo-*p*-xylene produced the 3-arylated indole as the exclusive product in 90% yield.

For the coupling of 2-methylindole, commercially available **5**[19b] is an effective ligand (Table 2, entries 4 and 5). Even under the best conditions, however, a large amount of C-arylated and overarylated products were obtained; only moderate yields of the desired product were obtained. In many cases when multiple indole products are formed, it was often difficult to cleanly separate the products by column chromatography.[16a]

For reactions of 2,3-dimethylindole, where competing arylation at the 3-position is not possible, we found that ligand **6**, also commercially available,[19b] is an effective ligand (Table 2, entries 14 and 15). As the substrate's nitrogen becomes increasingly hindered, as in the case of 2,3,7-trimethylindole, the reaction becomes slow; decomposition of the indole under the reaction conditions led to low yields of the desired product (average <40%).

In conclusion, the coupling of a wide variety of aryl halides and triflates with a wide range of indoles is described. With the proper choice of ligands, a variety of *N*-arylindoles may be obtained. Work is underway to ameliorate difficulties which remain, especially in finding catalysts that efficiently process hindered substrates.

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Supporting Information Available: Complete experimental procedures and spectral data for ligands **1**−**6** and the compounds listed in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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