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Direct Palladium-Catalyzed C-3 Arylation of Free (NH)-Indoles with Aryl Bromides under Ligandless Conditions

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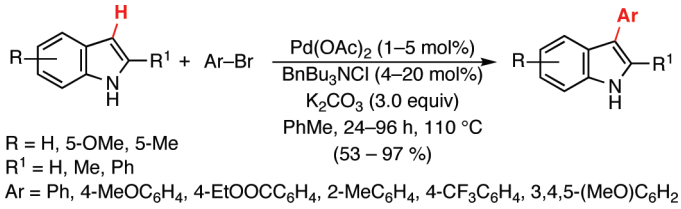
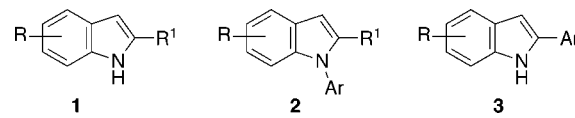


A new method for the efficient, practical, and highly regioselective direct palladium-catalyzed C-3 arylation of free (NH)-indole and its electron-rich 1-unsubstituted derivatives under ligandless conditions is described. The reactions, which are run outside a glovebox without purification of solvent and reagents, involve treatment of free (NH)-indoles with activated, unactivated, and deactivated aryl bromides in refluxing toluene in the presence of K_2CO_3 as the base and a catalyst system consisting of a combination of $Pd(OAc)_2$ and benzyl(tributyl)ammonium chloride. The experimental results are consistent with a catalytic cycle based on an electrophilic palladation pathway at the 3-position of 1-indolyl potassium salts.

Introduction

Indole scaffolds are frequently found in natural bioactive products, marketed drugs, functional materials, and agrochemicals.[1] Thus, considerable attention has been turned to the synthesis and selective functionalization of indoles over the years.[2] Recently, the development of efficient methods for the transition metal-catalyzed intermolecular direct arylation of free (NH)-indoles **1** with aryl halides has emerged as one of the most powerful synthetic methods to access indole derivatives. The procedures developed in the laboratories of Hartwig,[3] Watanabe,[4] and Buchwald[5] for the synthesis of 1-arylindoles **2** by *N*-arylation of indoles **1** with aryl halides involve the use of a phosphine ligand such as 1,1′-bis(diphenylphosphino)ferrocene (DPPF),[3a] 2,2′-bis-(diphenylphosphino)-1,1′-binaphthalene (BINAP),[3a] P(*t*-Bu)$_3$,[3b,4] or a biaryl(dialkyl)phosphine[5] in combination with a palladium compound such as $Pd(OAc)_2$,[3a,4] $Pd(dba)_2$,[3b] or $Pd_2(dba)_3$.[5] Unfortunately, these Pd-catalyzed reactions suffer from problems such as C-3 arylation and an intolerance of several important functional groups.[6a] Thus, more recently, they have been replaced by mild and highly efficient copper(I)-catalyzed[6] or $Fe(acac)_3$/CuO-cocatalyzed procedures.[7]



A great deal of attention has also been given to the Pd-catalyzed direct C-2 arylation of indoles **1** (R^1 = H) with

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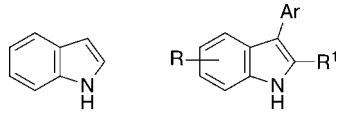
aryl halides[8–10] or diaryl iodonium tetrafluoroborates.[11,12] Such methods, which consist of regioselective C−H bond functionalization in the presence of a reactive NH functional group, enable direct access to free (NH)-2-arylindoles **3**, which are important structures serving as key components of a variety of bioactive compounds,[13] and represent significant progress compared with the conventional cross-coupling reactions. In fact, they do not necessitate the preparation of organometallic reagents and the subsequent disposal of the reaction coproducts containing the metallic subunit.[14,15] In 1985, Ohta and co-workers[8] described the first example of a Pd-catalyzed direct C-2 arylation of free (NH)-indole (**1a**) with chloropyrazines in the presence of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$/CuI as the catalyst and KOAc or K_2CO_3 as the base. On the other hand, we recently demonstrated that compounds **3** (R = H) can be prepared in low to moderate yields by highly regioselective Pd-catalyzed Cu-mediated C-2 arylation of **1a** with activated, unactivated, and deactivated aryl iodides under base-free and ligandless conditions.[9]



1a **4**

More recently, Sames and co-workers[10] described a phosphine-free Pd-catalyzed method for direct C-2 arylation of free (NH)-indoles with aryl bromides and iodides that provides the required 2-arylindoles **3** in low to satisfactory yields and accommodates both ortho-substituted aryl electrophiles and 3-substituted indoles. However, this method suffers from regioselectivity problems when the arylation reaction involves unsubstituted indole **1a**.[16] In 2006, Sanford and co-workers[11] designed a new protocol for the synthesis of indoles **3** based on Pd-catalyzed arylation of compounds **1** with diaryliodonium tetrafluoroborates. Interestingly, the method proved also to be useful for direct C-2 arylation of 1-methylindoles in high yields.[11] Finally, it is worth mentioning that even the use of a rhodium catalyst and cesium pivalate as the base has proved to be suitable for direct C-2 arylation of free (NH)-indoles,[17] but this system does not tolerate substrates containing a substituent at the 3-position of indole or at the ortho-position of the aryl halides.[17]

Several methods have also been described for the synthesis of 1-unsubstituted 3-arylindoles **4**,[18–21] but the preparation of these heterocycles by Pd-catalyzed direct C-3-arylation of free (NH)-indoles **1** has attracted less attention.[22,23] The scarcity of these studies might be explained taking into account that it has been reported that an electrophilic palladation of indole at the 3-position by an arylpalladium halide complex, which is formed by oxidative addition of an aryl halide to a catalytically active Pd(0) species, might be accompanied by a C3→C2 migration of an intermediate palladium species.[24] Nevertheless, in 2007, Zhang and co-workers[22] demonstrated that indoles **1** are able to undergo regioselective direct C-3 arylation when treated with aryl bromides **5** (1.1 equiv) and K_2CO_3 (3.0 equiv) in refluxing dioxane in the presence of 5 mol % of $Pd(OAc)_2(PPh_3)_2$ or 5 mol % of $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$. Unfortunately, this protocol proved to be unsuitable for electron-withdrawing or electron-donating substituted bromobenzenes, which were found to depress the arylation.[22] It is also worth noting that $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$, which is the commercially available catalyst precursor preferentially used in this protocol, is a quite expensive Pd complex.

Moreover, while this paper was in preparation, Cusati and Djakovitch reported a heterogeneously Pd-catalyzed procedure for the fully selective C-3 arylation of 2-substituted or 2-unsubstituted free (NH)-indoles with aryl bromides in refluxing dioxane in the presence of K_2CO_3 as the base and $[Pd(NH_3)_4]$/NaY as the catalyst.[23a] However, the protocol was unsatisfactory

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(16) The Pd-catalyzed reaction of indole with iodobenzene was found to give a 15/1 mixture of 2- and 3-phenylindole in 75% yield, whereas an analogous reaction with bromobenzene provided a 2:1 mixture of the same products in 28% yield.[10]

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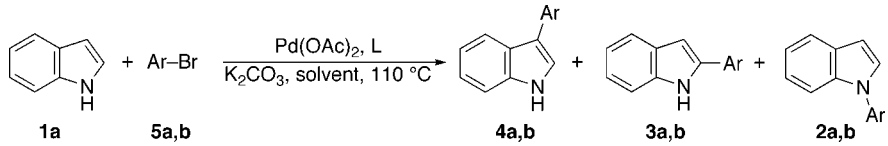
TABLE 1. Screening Reaction Conditions for the Regioselective C-3 Arylation of 1a with 5a,b



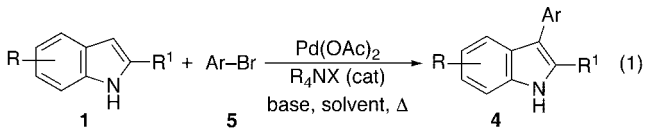
1a **5a,b** **4a,b** **3a,b** **2a,b**

	ArBr					products		
entry[a]	**5**	Ar	ligand	solvent	reaction time[b]	**4/3/2** GLC molar ratio	**4**, **3**, or **2**	yield (%)[c]
1[d]	**5a**	C_6H_5	PPh_3	dioxane	66	100:0:0	**4a**	70
2	**5a**	C_6H_5	PPh_3	DMF	48			
3[d]	**5a**	C_6H_5	P(2-furyl)$_3$	dioxane	24			
4	**5a**	C_6H_5	PPh_3	toluene	24	96:2:2	**4a**	80
5	**5a**	C_6H_5	PCy_3	toluene	96	90:3:7	**4a**	61
6[d]	**5b**	4-MeOC_6H_4	PPh_3	dioxane	48	97:2:1	**4b**	(57)[e]
7	**5b**	4-MeOC_6H_4	PPh_3	toluene	48	97:2:1	**4b**	60[e]
8	**5b**	4-MeOC_6H_4	P(2-furyl)$_3$	toluene	24			
9	**5b**	4-MeOC_6H_4	P(*o*-tolyl)$_3$	toluene	48			
10	**5b**	4-MeOC_6H_4	PCy_3	toluene	48	95:2:3	**4b**	57
11	**5b**	4-MeOC_6H_4	P(*t*-Bu)$_3$	toluene	48	0:0:100	**2b**	(34)
12	**5b**	4-MeOC_6H_4	P(*t*-Bu)$_2$Biph	toluene	48	0:0:100	**2b**	(62)
13	**5b**	4-MeOC_6H_4	PBu(1-Ad)$_2$	toluene	48	0:0:100	**2b**	(76)
14	**5b**	4-MeOC_6H_4	DPPF	toluene	48	93:3:4	**4b**	53[e]
15	**5b**	4-MeOC_6H_4	DPPP	toluene	48	98:2:0	**4b**	56[e]
16	**5b**	4-MeOC_6H_4	BINAP	toluene	48	96:3:1	**4b**	54
17	**5b**	4-MeOC_6H_4	Xantphos	toluene	48	76:21:3	**4b**	(6)[f]

[a] Unless otherwise reported the reactions were run at 110 °C (oil bath temperature) with 1 mmol of **1a**, 1.2 mmol of **5**, 5 mol % of Pd(OAc)$_2$, 10 mol % of a monodentate ligand, or 5 mol % of a bidentate ligand, 3.0 mmol of K_2CO_3 in 4 mL of solvent. [b] Unless otherwise reported the conversion of **1a** at the reported reaction time was higher than 96%. [c] Values in parentheses are referred to GLC yields. [d] This reaction was performed at 100 °C [e] The crude reaction mixture of this reaction was contaminated by a significant amount of **4a**. [f] The conversion of this reaction was ca. 22% after 48 h at 110 °C. Moreover, GLC analysis of the crude reaction mixture showed the presence of a significant amount of **4a**.

or did not provide the required arylation products when free (NH)-indole or 2-methyl- and 2-phenylindole were reacted with unactivated or deactivated aryl bromides.[23a] Noteworthy, Djakovitch and co-workers had previously reported that the selective Pd-catalyzed C-3 arylation of free (NH)-indole with aryl bromides can be achieved by the use of Pd(OAc)$_2$/$AgBF_4$ as the catalyst system,[23b] but the methodology was limited to the use of activated aryl bromides.[23b]

All these literature data and our continuing interest in the regioselective synthesis of arylazole derivatives by transition metal-catalyzed direct arylation[6h,9,12f,25] led us to look for new, efficient, and highly regioselective procedures for direct C-3 arylation of free (NH)-indoles **1** with aryl halides. In this paper we report the results of our studies in this field, which allowed us to develop a new effective protocol for the regioselective Pd-catalyzed C-3 arylation of indoles **1** with aryl bromides **5** that involves the use of a ligandless air-stable and cheap catalyst system consisting of a combination of Pd(OAc)$_2$ (1−5 mol %) and a lipophilic quaternary ammonium halide (4−20 mol %) (eq 1).



1 **5** **4** (1)

This catalyst system, as far as we are aware, has never been used in direct arylation of heteroarenes.[26] Moreover, unlike the protocols described by Zhang and co-workers[22] and Djakovitch and co-workers,[23] this new method allows for efficient and highly regioselective C-3 arylation of free (NH)-indoles, which include 2-substituted derivatives and indoles possessing an electron-donating group at the 5-position, with activated, unactivated, and deactivated aryl bromides.

Results and Discussion

We started our studies by attempting to improve the protocol developed by Zhang and co-workers.[22] Thus, we screened a variety of ligands and solvents for use in direct Pd-catalyzed C-3 arylation of free (NH)-indole (**1a**) with both an unactivated and a deactivated aryl bromide, bromobenzene (**5a**) and 4-bromoanisole (**5b**), respectively. As shown in Table 1, where the results of this screening are summarized, the arylation reactions were performed at 100−110 °C with use of 1.2 equiv of aryl bromide, 3.0 equiv of K_2CO_3, and a catalyst system consisting of a combination of 5 mol % of Pd(OAc)$_2$ and 10 mol % of a monodentate ligand, L, such as PPh_3, P(2-furyl)$_3$, $AsPh_3$, P(*o*-tolyl)$_3$, P(*t*-Bu)$_3$, 2,2′-bis(di-*tert*-butylphosphino)-1,1′-biphenyl [P(*t*-Bu)$_2$Biph], butyldi-1-adamantylphosphine [PBu(1-Ad)$_2$], and PCy_3, or 5 mol % of a bidentate phosphine ligand such as 1,3-diphenylphosphinopropane (DPPP), DPPF, BINAP, or 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos). The first reaction that we examined involved treatment of **1a** with **5a** under experimental conditions similar to those used in the literature for reaction of **1a** with **5a**, using [(*t*-

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(26) Recently, a combination of a Pd(II) derivative, $PdCl_2(PhCN)_2$, and a lipophilic quaternary ammonium salt, $BnBu_3NCl$, has been employed for the Mirozoki−Heck type arylation of alkenes with aroyl chlorides under base-free conditions [Sugihara, T.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2005**, *46*, 8269−8271].

TABLE 2. Palladium-Catalyzed Direct C-3 Arylation of Indoles 1, 3a, and 1-Methylindole (6) with Aryl Bromides 5 under Ligandless Conditions

	indole			Ar−Br			product	
entry[a]	**1**, **3** or **6**	R	R^1	**5**		reaction time (h)[b]	**4**	yield (%)[c]
1[d]	**1a**	H	H	**5b**	4-$MeOC_6H_4$	48	**4b**	(56)
2	**1a**	H	H	**5b**	4-$MeOC_6H_4$	24	**4b**	73
3	**1a**	H	H	**5a**	C_6H_5	24	**4a**	97
4	**1a**	H	H	**5e**	4-$EtOOCC_6H_4$	46	**4c**	67
5	**1a**	H	H	**5d**	3,4,5-$(MeO)_3C_6H_2$	48	**4d**	93
6	**1a**	H	H	**5h**	2-MeC_6H_4	48	**4e**	81
7	**1a**	H	H	**5i**	4-$CF_3C_6H_4$	24	**4f**	80
8[e]	**1a**	H	H	**5a**	C_6H_5	96	**4a**	53
9	**1a**	H	H	**5g**	4-$NO_2C_6H_4$	48		
10	**1b**	H	Me	**5b**	4-$MeOC_6H_4$	48	**4g**	62
11	**3a**	H	C_6H_5	**5b**	4-$MeOC_6H_4$	24	**4h**	74
12	**6**	1-Me	H	**5b**	4-$MeOC_6H_4$	48		
13	**1c**	5-MeO	H	**5b**	4-$MeOC_6H_4$	48	**4i**	75
14	**1d**	5-CN	H	**5b**	4-$MeOC_6H_4$	96		
15	**1e**	H	COOEt	**5b**	4-$MeOC_6H_4$	48		
16	**1f**	5-Me	H	**5b**	4-$MeOC_6H_4$	24	**4j**	78

[a] Unless otherwise reported the reactions were run at 110 °C (oil bath temperature) with 1 mmol of **1**, **3a**, or **6**, 1.2 mmol of **5**, 5 mol % of $Pd(OAc)_2$, 20 mol % of $BnBu_3NCl$, 3.0 mmol of K_2CO_3 in 4 mL of toluene. [b] Unless otherwise reported the conversion of indoles **1** or **3** was higher than 97%. [c] Values in parentheses are referred to GLC yields. [d] This reaction was performed with 20 mol % of $BnEt_3NCl$. [e] This reaction was performed with 1 mol % of $Pd(OAc)_2$ and 4 mol % of $BnBu_3NCl$.

$Bu)_2P(OH)]_2PdCl_2$as the catalyst precursor.[22] As shown in entry 1 of Table 1, the reaction performed in dioxane at 100 °C gave regioselectively 3-phenylindole (**4a)** in a yield (70%) very similar to that reported in the literature.[22] Interestingly, the reaction conditions of this entry proved to be suitable for the synthesis of 3-(4-methoxyphenyl)indole (**4b**) in 57% GLC yield from **1a** and **5b** (entry 6, Table 2), thus demonstrating that **1a** can efficiently undergo Pd-catalyzed C-3 arylation also with a deactivated aryl bromide.

However, the crude reaction mixture of this entry was found to be contaminated by small amounts of 2- and 1-arylindole, **3b** and **2b**, respectively, and a significant amount of the phenyl coupling product **4a** that very likely derived from a scrambling reaction involving the ligand and **5b**.[27] Remarkably, compounds **4a** and **4b** were obtained in yields (80% and 60%, respectively) higher than that obtained in entries 1 and 6 in Table 1, respectively, when the reactions of **1a** with **5a** and **5b** were carried out in refluxing toluene (entries 4 and 7, Table 1). On the contrary, the arylation reaction did not occur when DMF was used as the solvent (entry 2, Table 1) or when $P(2\text{-furyl})_3$ or $P(o\text{-tolyl})_3$ were employed as ligands (entries 3, 8, and 9, Table 1). We also observed that no scrambling reaction between the ligand and **5b** occurred when the ligand of the catalyst system was PCy_3. In addition, the arylation of **1a** with **5b**, when run in toluene in the presence of this ligand, furnished a mixture of **4b**, **3b**,[28] and **2b**[28] in a 95:2:3 molar ratio, respectively, from which **4b** was isolated in 57% yield (entry 10, Table 1). Similar reaction conditions allowed for the synthesis of **4a** in 61% yield (entry 5, Table 1).

Among the tested bidentate phosphine ligands for the reaction between **1a** and **5b**, the best results were obtained when BINAP was employed as the ligand; in fact, **4b** was isolated in a yield (54%) very similar to that obtained with PCy_3 as the ligand (compare entries 16 and 10, Table 1). Satisfactory chemical yields of **4b** were also obtained by treatment of **1a** with **5b** with DPPF or DPPP as ligands (entries 14 and 15, Table 1), but significant amounts of **4a** derived from a scrambling reaction were found to be present in the crude reaction mixtures. On the other hand, totally unsatisfactory results were obtained with Xantphos as the ligand (entry 17, Table 1). It is also worth mentioning that the regioselectivity of the reaction carried out with DPPF as the ligand proved to be different from that of the Pd-catalyzed arylations described by Hartwig and co-workers[3a] where *N*-arylindoles **2** are produced by treatment of toluene solutions of **1a** and aryl bromides that possess an electron-withdrawing group at the para-position, in the presence of Cs_2CO_3 and catalytic amounts of $Pd(OAc)_2$ and DPPF. However, we observed that 1-arylation instead of C-3 arylation of **1a** with **5b** occurred when an electron-rich and bulky phosphine ligand such as $P(t\text{-Bu})_3$, $P(t\text{-Bu})_2$Biph, or $PBu(1\text{-Ad})_2$ was used in place of PCy_3 (entries 10, 11, and 12, respectively, Table 1). The reactions under these conditions produced **2b** in low to satisfactory GLC yields.

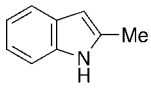
We then probed the performance of bases different from K_2CO_3 in the Pd-catalyzed arylation of **1a** with **5b** in refluxing toluene in the presence of the $Pd(OAc)_2/PCy_3$ catalyst system and found that the tested bases, which included Cs_2CO_3, Na_2CO_3, KOAc, CsOAc, $NaHCO_3$, and $KHCO_3$, gave very unsatisfactory results as regards both the conversion of the reaction after 48 h and its regioselectivity. Unfortunately, unsatisfactory yields were also obtained when the scope of the $Pd(OAc)_2/PCy_3$-catalyzed C-3-arylation of **1a**, 2-methylindole (**1b**), and 2-phenylindole (**3a**) in refluxing toluene with aryl bromides **5c**−**g** was tested.

On the basis of all these results, which illustrated the nonbeneficial role of the ligands on the outcome of the Pd-

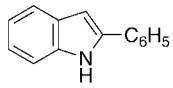
(27) For the formation of similar byproducts in the C-5 arylation of 1-aryl-1*H*-imidazoles with aryl iodides in DMF in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and Cs_2CO_3 (2.0 equiv), see ref 25a.

(28) Authentic samples of **3b** and **2b** were prepared according to the procedures reported in refs 9b and 6h, respectively.

(29) For previous examples of Pd-catalyzed C−H arylation reactions under ligandless conditions, see: (a) Majumdar, K. C.; Chattopadhyay, B.; Nath, S. *Tetrahedron Lett.* **2008**, *49*, 1609–1612. (b) Reference 10. (c) Shen, D.-M.; Liu, C.; Chen, Q.-Y. *J. Org. Chem.* **2006**, *71*, 6508–6511. (d) Reference 9a. (e) References 25b,c,e. (f) Maehara, A.; Satoh, T.; Miura, M. *Tetrahedron* **2008**, *64*, 5982–5986. (g) Spencer, J.; Chowdhry, B. Z.; Mallet, A. I.; Rathnam, R. P.; Adatia, T.; Bashall, A.; Rominger, F. *Tetrahedron* **2008**, *64*, 6082–6089.



1b



3a

Ar-Br

5c : Ar = 4-MeC_6H_4
5d : Ar = 3,4,5-$(MeO)_3C_6H_2$
5e : Ar = 4-$EtOOCC_6H_4$
5f : Ar = 3,4-$(MeO)_2C_6H_3$
5g : Ar = 4-$NO_2C_6H_4$

catalyzed arylation of indoles **1** with aryl bromides, we then attempted to perform direct C-3 arylation of compounds **1** in toluene in the presence K_2CO_3 as the base and a catalytic amount of $Pd(OAc)_2$ under ligandless conditions.[29] In fact, we surmised that $Pd(OAc)_2$ could undergo thermolytic decomposition in refluxing toluene with formation of catalytically active Pd(0) nanoparticles.[30] At first, we tried to determine the best conditions for the $Pd(OAc)_2$-catalyzed reaction of **1a** with **5b**, but we found that, when this reaction was performed in refluxing toluene for 48 h in the presence of K_2CO_3 as the base using **1a** and **5b** in a 1:1.2 molar ratio, **4b** was obtained in a low conversion (50%) and in 37% GLC yield and 96% regioselectivity. We next thought it right to ascertain whether this result could be significantly improved by using a catalyst system consisting of a combination of $Pd(OAc)_2$ (1−5 mol %) and a lipophilic quaternary ammonium salt such as benzyl(triethyl)ammonium chloride ($BnEt_3NCl$) or benzyl(tributyl)ammonium chloride ($BnBu_3NCl$) (4−20 mol %). It is known in fact that lipophilic quaternary ammonium salts are able to stabilize soluble Pd clusters and to slow down markedly their conversion to inactive Pd black.[31] Moreover, Pd clusters stabilized by quaternary ammonium salts have been reported to be active catalysts in the Heck reaction on aryl bromides.[32] Thus, the reaction of **1a** with **5b** in refluxing toluene in the presence of 3.0 equiv of K_2CO_3 and a catalyst system consisting of 5 mol % of $Pd(OAc)_2$ and 20 mol % of $BnEt_3NCl$ was examined. This arylation proved to be fully regioselective and gave **4b** in 56% GLC yield (entry 1, Table 2). Interestingly, an attempt to improve the yield of this reaction by using $BnBu_3NCl$ (20 mol %) as additive in place of less lipophilic $BnEt_3NCl$ proved to be successful and the reaction performed under argon outside a glovebox with this quaternary ammonium salt gave **4b** in 73% isolated yield (entry 2, Table 2); however, the required arylation product was not obtained when the reaction was performed in the absence of K_2CO_3.

Next, the protocol used in entry 2 of Table 2 was investigated for the regioselective C-3 arylation of indoles **1a**−**f**, **3a**, and **6** with a variety of activated, unactivated, and deactivated aryl bromides **5**. Unactivated bromides included bromobenzene (**5a**) and an ortho-substituted derivative, 2-bromotoluene (**5h**), and activated bromides included ethyl 4-bromobenzoate (**5e**), 1-bromo-4-(trifluoromethyl)benzene (**5i**), and 1-bromo-4-nitrobenzene (**5g**). On the other hand, 5-bromo-1,2,3-trimethoxybenzene (**5d**) was used as a strongly deactivated aryl bromide. The arylation reactions involving free (NH)-indole (**1a**) and bromides **5a** (entry 3), **5e** (entry 4), **5d** (entry 5), **5h** (entry 6), and **5i** (entry 7) occurred in high yields and, notably, proved to be very clean. In fact, the reaction mixtures contained no regioisomers of the required 3-arylindoles **4**. However, unexpectedly, no C- or N-arylation product was obtained in the reaction of **1a** with **5g** (entry 9, Table 2).

Interestingly, when a catalyst loading lower than that of entries 2−7 in Table 2 was used, i.e., 1 mol % of $Pd(OAc)_2$ and 4 mol % of $BnBu_3NCl$, catalysis still occurred for the reaction of **1a** with **5a** (entry 8, Table 2), but the reaction rate and yield were markedly reduced.

Table 2 also illustrates that, as we had hoped for, the reaction conditions of entries 2−7 for direct arylation of **1a** were found to be suitable for the efficient and totally regioselective C-3 arylation of electron-rich free (NH)-indoles including 2-methylindole (**1b**), 2-phenylindole (**3a**), 5-methoxyindole (**1c**), and 5-methylindole (**1f**) with bromide **5b** (entries 10, 11, 13, and 16, respectively). On the contrary, attempts to obtain the required C-3 arylation products by the Pd-catalyzed reaction of 1-methylindole (**6**) (entry 12, Table 2) or free (NH)-indoles that possess an electron-withdrawing substituent (entries 14 and 15, Table 2) proved to be unsuccessful. In fact, the reaction mixtures which were obtained from the Pd-catalyzed reactions of **5b** with **6**, indole-5-carbonitrile (**1d**), and ethyl indole-2-carboxylate (**1e**) contained only the unreacted starting materials.

Conclusions

We have at first demonstrated that a combination of $Pd(OAc)_2$ and PCy_3 can be used as a catalyst in the highly regioselective direct C-3 arylation of free (NH)-indole (**1a**) with bromobenzene (**5a**) and 4-bromoanisole (**5b**) in toluene in the presence of K_2CO_3 as the base. We have also found that when bulky and electron-rich phosphines such as P(*t*-Bu)$_3$, P(*t*-Bu)$_2$Biph, and PBu(1-Ad)$_2$ are used in place of PCy_3 arylation of **1a** with **5b** occurs at the 1-position with complete regioselectivity. However, the $Pd(OAc)_2/PCy_3$ catalyst system has proved to be unsuitable for efficient arylation of **1a** with aryl bromides different from **5a** and **5b**.

We have then modified significantly this catalyst system and have succeeded in the development of a new and practical protocol for the efficient and fully regioselective C-3 arylation of free (NH)-indoles **1**, including derivatives that possess an electron-rich substituent, with aryl bromides. The clean arylation reactions, which are run under ligandless conditions outside a glovebox without purification of solvent and reagents, involve treatment of compounds **1** with a small molar excess of activated, unactivated, and deactivated aryl bromides in refluxing toluene in the presence of K_2CO_3 and catalytic amounts of $Pd(OAc)_2$ and $BnBu_3NCl$ and furnish the required free (NH)-3-arylindoles in satisfactory to good yields, thereby providing a useful tool in organic synthesis.

Significantly, this new protocol does not allow C-3 arylation of 1-methylindoles and free (NH)-indoles containing an electron-withdrawing substituent. Thus, it is consistent with a reaction mechanism that presumably involves an electrophilic palladation at the 3-position of 1-indolyl potassium salts derived from the

(30) It has been reported that in the thermolysis of $Pd(OAc)_2$, the acetate group serves as the reductant in a process, which generates Pd(0) in addition to CO_2, methane, and ethane: (a) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165−168. (b) Reetz, M. T.; Maase, M. *Adv. Mater.* **1999**, *11*, 773–777.

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(32) (a) Sugihara, T.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2005**, *46*, 8269–8271. (b) Reference 30a. (c) Reetz, M. T.; Breinbauer, R.; Wanninger, K. *Tetrahedron Lett.* **1996**, *37*, 4499–4502. (d) Beller, M.; Fischer, H.; Kühlein, K.; Reisinger, C.-P; Herrmann, W. A. *J. Organomet. Chem.* **1996**, *520*, 257–259.

(33) The mechanistic pathway for Pd-catalyzed arylation of electron-rich heterocycles is currently believed to involve an electrophilic attack of arylpalladium species at the heterocycle: (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473. (b) Reference 23b. (c) Reference 24. (d) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159–1162.

reaction of free (NH)-indoles with K_2CO_3 in refluxing toluene.[33] It is also worth mentioning that, in contrast to what was reported by Sames and co-workers for the C-2 arylation reaction of 1-substituted indoles with aryl iodides in DMA using the $Pd(OAc)_2/PPh_3/CsOAc$ system,[24] this C-3 palladation is not accompanied by a 1,2-migration of an intermediate palladium species and seems to require a strongly electron-rich C-3 position in the heterocyclic substrate. However, our next goal is to clarify the reaction mechanism of the Pd-catalyzed C-3 arylation of free (NH)-indoles under ligandless conditions.

Experimental Section

Typical Procedure for C-3 or N-1 Arylation of Free (NH)-Indole (1a) with Bromobenzene (5a) and 4-Bromoanisole (5b) in the Presence of a Combination of $Pd(OAc)_2$ and a Phosphine as a Catalyst. To a flame-dried reaction vessel were added compound **1a** (0.117 g, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), K_2CO_3 (0.415 g, 3.0 mmol), and a phosphine ligand (0.1 mmol of a monodentate ligand or 0.05 mmol of a bidentate ligand). The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon and this sequence was repeated three times. Solvent (4 mL) and bromide **5a** (0.188 g, 1.2 mmol) or **5b** (0.225 g, 1.2 mmol) were then added successively under a stream of argon at room temperature. The resulting mixture was refluxed under argon for the period of time reported in Table 1. The completion of the reaction and composition of the reaction mixture were established on the basis of TLC, GLC, and GLC-MS analyses of a sample of the reaction mixture diluted with AcOEt and filtered through Celite. After being cooled to room temperature, the reaction mixture was diluted with AcOEt and filtered through Celite. The filtrate was analyzed by GLC and concentrated under reduced pressure. The residue obtained from the reactions of entries 1, 4, 5, 7, 10, 14, 15, and 16 of Table 1 was purified by MPLC on silica gel. Table 1 summarizes the results of the Pd-catalyzed arylations of **1a** with bromides **5a**,**b**.

1-Phenylindole (**2a**), which was found to be present in the crude reaction mixture of entries 4 and 5 of Table 1, was identified by comparison of its EI-MS spectrum and GLC retention time with those of an authentic sample of **2a** synthesized according to the literature.[6h] 1-(4-Methoxyphenyl)indole (**2b**) obtained in the Pd-catalyzed reactions performed in the presence of P(*t*-Bu)$_3$, P(*t*-Bu)$_2$Biph, and PBu(1-Ad)$_2$ as phosphine ligands (entries 11, 12, and 13, respectively, Table 1) was identified by comparison of its GLC retention time and EI-MS spectrum with those of an authentic sample prepared according to the literature.[6h] 2-Phenylindole (**3a**), which was found to be present in the crude reaction mixture of entries 4 and 5 of Table 1 and 2-(4-methoxyphenyl)indole (**3b**), which contaminated the reaction mixtures of entries 6, 7, and 14−17, of Table 1, were identified by comparison of their GLC retention times and EI-MS spectra with those of authentic samples of these compounds prepared according to the literature[9b] by $Pd(OAc)_2$-catalyzed and CuI-mediated C-2 arylation of **1a** with iodobenzene and 4-iodoanisole, respectively. The crude reaction product obtained in entry 4 of Table 1 with PPh_3 as the ligand was purified by MPLC on silica gel with a mixture of toluene and petroleum ether (80:20) as eluent to give 3-phenylindole (**4a**) (0.154 g, 80%) as a white solid: mp 85−87 °C. EI-MS *m*/*z* 194 (15), 193 (100), 192 (15), 166 (5), 165 (26). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.39 (m, 7H). The spectral properties of this compound were in good agreement with those previously reported.[34] On the other hand, the crude reaction product obtained in entry 10 of Table 1 with PCy_3 as a ligand was purified by MPLC on silica gel with a mixture of toluene and petroleum ether (90:10) as eluent to give 3-(4-methoxyphenyl)indole (**4b**) (0.146 g, 57%) as a light yellow solid: mp 128−131 °C. EI-MS *m*/*z* 224 (17), 223 (100), 222 (8), 208 (90), 180 (17). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.57 (m, 2H), 7.36 (m, 1H), 7.20 (m, 3H), 6.99 (m, 2H), 3.84 (s, 3H). The spectral properties of this compound were in agreement with those previously reported.[34]

Typical Procedure for Direct C-3 Arylation of Free (NH)-Indoles 1 and 3a with Aryl Bromides 5 in the Presence of the $Pd(OAc)_2/BnBu_3NCl/K_2CO_3$ System. To a flame-dried reaction vessel were added a free (NH)-indole **1** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), K_2CO_3 (0.415 g, 3.0 mmol), and $BnBu_3NCl$ (62.4 mg, 0.20 mmol). The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon three times. Toluene (4 mL) and a bromide **5** (1.2 mmol) were then added successively under a stream of argon at room temperature and the resulting mixture was refluxed under argon for the period of time reported in Table 2. Free (NH)-indoles used in this procedure included **1a**, 2-methylindole (**1b**), 2-phenylindole (**3a**), 5-methoxyindole (**1c**), indole-5-carbonitrile (**1d**), ethyl indole-2-carboxylate (**1e**), and 5-methylindole (**1f**). On the other hand, aryl bromides **5** included **5a**, **5b**, ethyl 4-bromobenzoate (**5e**), 2-bromotoluene (**5h**), 1-bromo-4-(trifluoromethyl)benzene (**5i**), and 1-bromo-4-nitrobenzene (**5g**). The completion of the arylation reactions and composition of the reaction mixtures were established on the basis of TLC, GLC, and GLC-MS analyses of a sample of the reaction mixture diluted with AcOEt and filtered through Celite. After being cooled to room temperature, the reaction mixtures were diluted with AcOEt and filtered through Celite. The filtrates were concentrated under reduced pressure and the residues were purified by MPLC on silica gel. As shown in Table 2, this procedure allowed the efficient and direct C-3 arylation of **1a** with bromides **5b**, **5a**, **5e**, **5d**, **5h**, and **5i** (entries 2−7, Table 2) and of indoles **1b**, **3a**, **1d**, and **1g** with **5b** (entries 10, 11, 13, and 16, Table 2, respectively), but it proved to be unsuitable for arylation of **1a** with **5g** (entry 9), and of indoles **1d** and **1e** with **5b** (entries 14 and 15, Table 2, respectively). 3-Arylindoles **4d**, **4e**, and **4i** are representative of those prepared with this procedure.

3-(3,4,5-Trimethoxyphenyl)indole (4d). The crude reaction product, which was obtained in entry 5 of Table 2 by Pd-catalyzed reaction of **1a** with **5d**, was purified by MPLC on silica gel with a mixture of toluene and AcOEt (70:30) as eluent to give **4d** (0.263 g, 93%) as a pale yellow solid: mp 112−114 °C. EI-MS *m*/*z* 284 (19), 283 (100), 269 (18), 207 (19). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.91 (m, 1H), 7.43 (m, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.23 (m, 2H), 6.87 (s, 2H), 3.93 (s, 6H), 3.92 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.6 (2C), 136.7, 131.3, 125.8, 122.7, 122,5, 121.6, 120.3, 119.6, 118.5, 111.5 (2C), 60.9, 56.3 (2C). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.00; H, 5.96; N, 4.83.

3-(2-Methylphenyl)indole (4e). The crude reaction product, which was obtained in entry 6 of Table 2 by Pd-catalyzed reaction of **1a** with **5h**, was purified by MPLC on silica gel with a mixture of toluene and petroleum ether (60:40) as eluent to give **4e** (0.168 g, 81%) as a light yellow oil. EI-MS *m*/*z* 208 (14), 207 (96), 206 (100), 204 (20), 178 (20). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (br, s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.41 (m, 2H), 7.24 (m, 6H), 2.31 (s, 3H).). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.9, 135.9, 134.5, 130.9, 130.3, 127.2, 126.7, 125.6, 122.7, 122.2, 120.2, 119.8, 117.6, 111.2, 20.6. The physical and spectral properties of this compound were in agreement with those previously reported.[35]

5-Methoxy-3-(4-methoxyphenyl)indole (4i). The crude reaction product, which was obtained in entry 13 of Table 2 by Pd-catalyzed reaction of **1c** with **5b**, was purified by MPLC on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **4i** (0.190 g, 75%) as a light yellow solid: mp 74−76 °C. EI-MS *m*/*z* 254 (18), 253 (100), 239 (11), 238 (67), 210 (12). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.55 (m, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.22 (m, 1H), 7.00 (m, 2H), 6.90 (dd, J

(34) Kasahara, T.; Kondo, Y. *Heterocycles* **2006**, *67*, 95–100.

= 8.6 and 2.4 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.0, 154.6, 131.7, 128.5 (2C), 126.2, 122.0, 117.7, 114.3 (2C), 112.5, 112.3, 112.2, 101.5, 56.0, 55.3. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.62; H, 5.84; N, 5.46.

(35) Pathak, R.; Nhlapo, J. M.; Govender, S.; Michael, J. P.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2006**, *62*, 2820–2830.

Acknowledgment. We thank the University of Pisa for financial support.

Supporting Information Available: Experimental procedures and characterization for compounds **4c**, **4f**−**4h**, and **4j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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