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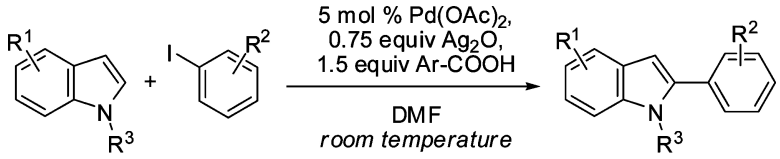

R^1, R^2 = -OH, -CH_2OH, -CHO, -Br, -CN, ...

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Room Temperature and Phosphine Free Palladium Catalyzed Direct C-2 Arylation of Indoles

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Direct C−H functionalization has emerged over the past few years as an attractive strategy to enhance molecular complexity.[1] However, in spite of major advances in this field, the important aryl−aryl bond formation is still almost exclusively carried out by traditional cross-coupling reactions, which require a differential prefunctionalization of both aryl coupling partners.[2] Indeed, the few currently available methods for direct C−H arylation suffer from the need for drastic conditions, elevated temperatures (125 to 150 °C), and long reaction times (24 to 48 h) which significantly limit their scope and functional group tolerance. Recently an elegant methodology for the C-2 arylation of indoles based on a $Pd^{II/IV}$ cycle that allows the use of lower temperatures (room temperature to 80 °C) has been reported.[3] However, this oxidative approach suffers the limitation of requiring noneasily accessible iodine(III) arylating reagents. Therefore, a milder methodology able to carry out the direct arylation at *room temperature* with the extensive pool of commercially available aryl iodides would be highly desirable.

Since indoles are ubiquitous among biologically active natural products and pharmaceutical compounds, their arylation reactions are of considerable importance.[3−5] The limiting step in the arylation of indoles in a $Pd^{0/II}$ catalytic cycle is believed to be the electrophilic palladation of the electron-rich palladium(II) species **I** (path a, Scheme 1).[4g] Silver(I) salts are commonly employed to abstract halide anions from transition metal complexes thus rendering them more electrophilic.[6] Therefore, we reasoned that by using an appropriate silver(I) salt to remove the iodide from the palladium-(II) complex **I**, a cationic palladium species (**IV**), which would be more electrophilic toward the indole unit (Ar′-H), could be generated, thus increasing the rate of the palladation step (path b). Initially, silver-mediated ligand metathesis of **I** would afford complex **III**. The crucial choice of a relatively poorly coordinating carboxylate as the counterion should allow the dissociation to the cationic species **IV** in catalytically useful amounts.[7] At the same time, the carboxylate would act as a base in the electrophilic palladation step.[8] We report here a methodology based on this reasoning which allows the direct arylation of indoles at room temperature under very mild conditions.

As a starting point, we analyzed the coupling between *N*-methylindole (**1**) and iodobenzene (**2**, Table 1). In order to easily test several silver(I) carboxylates, a procedure to generate them *in situ* from Ag_2O (0.75 equiv) and the corresponding carboxylic acid (1.5 equiv) was employed (compare entries 2 and 4). The substitution on the carboxylic acid had a dramatic effect on the efficiency of the reaction, showing an inverse correlation with its pK_a (entries 5−9). *ortho*-Nitrobenzoic acid was found to be the best carboxylic acid, affording the C-2 arylation adduct **3** with complete conversion and a remarkable 92% isolated yield after 7 h at *room temperature* (entry 9).

We next examined the scope of the reaction with a variety of differently substituted aryl iodides. As shown in Table 2, excellent

Scheme 1. Working Hypothesis: Highly Activated Palladium(II) Species for C−H Arylation

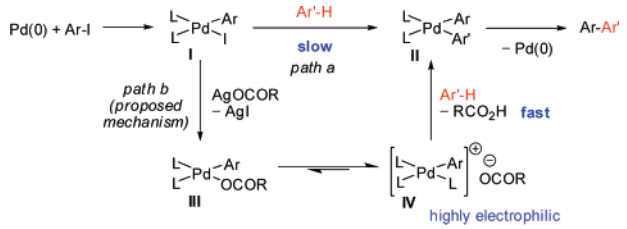
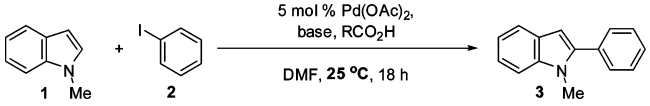


Table 1. Optimization of the Room Temperature Coupling between *N*-Methylindole (**1**) and PhI (**2**)[a]



entry	base	acid	conv (%)[b]
1	K_2CO_3	none	<5
2	AgOAc	none	53
3	Ag_2O	none	12
4	Ag_2O	CH_3CO_2H	49
5	Ag_2O	*o*-MeO−C_6H_4−CO_2H	13
6	Ag_2O	*o*-Me−C_6H_4−CO_2H	51
7	Ag_2O	*o*-Ph−C_6H_4−CO_2H	95
8	Ag_2O	*p*-O_2N−C_6H_4−CO_2H	81
9[c]	Ag_2O	*o*-O_2N−C_6H_4−CO_2H	>99

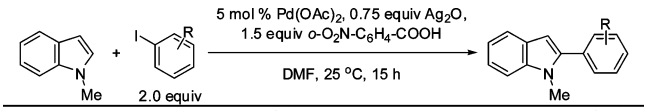
[a] Unless otherwise noted, all reactions were carried out using 5 mol % $Pd(OAc)_2$, 1.5 equiv (entries 1−2) or 0.75 equiv (entries 3−9) of base, 1.5 equiv of acid, 1.0 equiv of **1** and 2.0 equiv of **2** in a 0.5 M solution, for 18 h at 25 °C. [b] Conversion measured by GC using an internal standard. [c] The reaction was carried for 7 h.

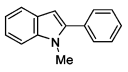
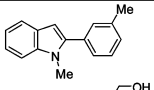
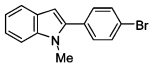
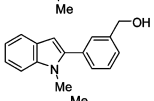
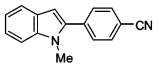
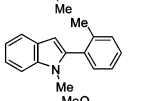
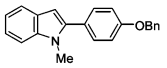
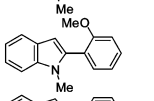
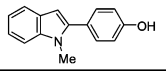
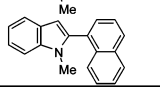
yields are obtained in the reaction of *N*-methylindole with several aryl iodides. Both, electron-withdrawing (entries 2 and 3) and electron-donating substitutents (entries 4−9) are suitable. The reaction conditions are compatible with nitriles, ethers and, remarkably, even with bromides and unprotected benzylic alcohols (entries 2 and 7) that could be easily substituted or oxidized under harsher conditions. Even the more acidic phenol group (entry 4) was also found to be compatible with the reaction conditions. It is noteworthy that most of the substrates afford quantitative conversion to products greatly facilitating the purification process. In addition, no C-3 arylation was observed in any of the examples.[9] As expected, the more hindered *ortho*- substituted aryl iodides react considerably more slowly than the *meta*- and *para*- counterparts and afford slightly lower yields (entries 8−10). Notably, the highly reactive 2-(*o*-methoxyphenyl)-*N*-methylindole is obtained in moderate yields under these mild conditions (entry 9).

We next examined the substitution in the heteroarene moiety (see Table 3). Gratifyingly, the methyl group in the nitrogen of the indole can be replaced for a benzyl group without affecting the yield (entry 1). Interestingly, free N−H-indoles are less reactive

10.1021/ja710731a CCC: $40.75

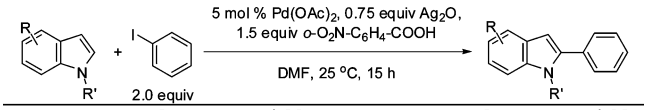
Table 2. Scope of C-2 Arylation of *N*-Methylindole

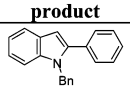
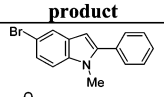
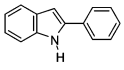
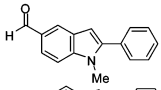
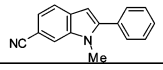
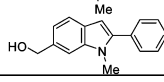


entry	product	yield	entry	product	yield
1[a]		92%	6		92%
2		99%	7		87%
3		91%	8[b]		62%
4		95%	9[c]		58%
5		82%	10		76%

[a] The reaction was carried out for 7 h. [b] The reaction was carried out for 24 h. [c] The reaction was carried out with 5 equiv of the iodoarene for 38 h.

Table 3. C-2 Arylation of Functionalized Indoles



entry	product	yield	entry	product	yield
1		84%	4		90%
2[a]		61%	5		88%
3[b]		91%	6		95%

[a] The reaction was carried out at 50 °C for 38 h. [b] The reaction was carried out using 10 mol % $Pd(OAc)_2$.

under this system (entry 2) requiring 38 h at 50 °C to afford 62% of the C-2 arylated product. As for the substitution on the benzene ring of the indole unit, it can incorporate a wide array of functional groups such as nitrile, bromide, aldehyde, and benzylic alcohol (entries 3−6).

Mechanistically both a $Pd^{0/II}$ and a $Pd^{II/IV}$ catalytic cycle are conceivable. A $Pd^{II/IV}$ cycle has been suggested in a related C−H arylation system using silver acetate in acetic or trifluoroacetic acid as the solvent but at much higher temperatures (120 to 140 °C).[10] Otherwise, removal of iodide from a palladium(II) species by Ag_2O has also been suggested in other cross-coupling processes.[11] In our system, the mechanistic rationale must account for the important role of the base. Indeed, the counterintuitive inverse correlation between the pK_a of the conjugated acid and catalytic activity is consistent with the hypothesis suggested in Scheme 1. Furthermore, an important solvent specificity for the highly coordinating DMF was found.[12] This would be explained in terms of an easier formation of cationic species **IV**.[13]

In conclusion, we have developed a new methodology that allows for the first time the direct C-2 arylation of indoles with aryl iodides *at room temperature without the presence of phosphines or other ligands*. These mild conditions permit a broad set of functionalities both in the indole and in the aryl iodide units, and a variety of novel compounds have been prepared in excellent yields. Mechanistic studies toward the understanding of the catalytic cycle are under way.

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Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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