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Room Temperature Palladium-Catalyzed 2-Arylation of Indoles

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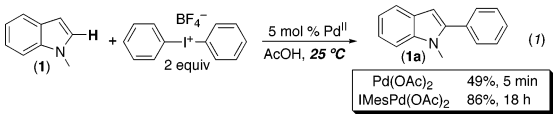
2-Arylindoles are important structures that serve as key components of a variety of biologically active molecules.[1,2] Many traditional approaches to these compounds have involved cross-coupling between a 2-functionalized indole and a functionalized arene derivative—a strategy that often requires multistep synthesis of the indole fragment.[1] In contrast, recent work has focused on the development of transition metal-catalyzed methods for the direct arylation of indoles[2−4] and related heterocycles.[5] Most typically, such arylations involve coupling between an aryl halide and an electron-rich *N*-alkyl or *N*-anionic indole derivative via a $Pd^{0/II}$ catalytic cycle.[2] While these reactions are often synthetically useful, they suffer from several notable disadvantages, including (i) the requirement for very high temperatures and long times (typically 125−150 °C for 12−48 h),[2a−c] (ii) the need for special conditions (often strong bases) for the arylation of unprotected indoles,[2a−c] (iii) variable levels of selectivity for arylation at the 2-position versus the 3-position,[2a] and (iv) moderate scope and functional group tolerance as well as high sensitivity to ambient air and moisture.

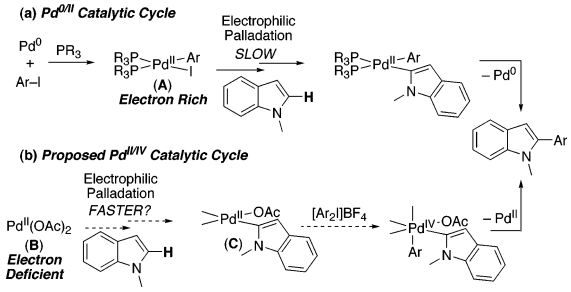
We felt that many of these limitations (particularly the need for high temperatures) were a direct consequence of the $Pd^{0/II}$ mechanism of these reactions. As summarized in Scheme 1a, the turnover limiting step of such $Pd^{0/II}$ catalytic cycles is believed to involve electrophilic indole palladation by a highly electron-rich bisphosphine Pd^{II} σ-aryl species (**A**).[2a] We reasoned that the rate of this key palladation step should be greatly enhanced by the use of a more electron-deficient Pd^{II} catalyst (e.g., $Pd(OAc)_2$),[4] and that the resulting σ-indole Pd^{II} complex (**C**) might undergo subsequent oxidative arylation with $[Ar-I-Ar]BF_4$ via an alternative $Pd^{II/IV}$ cycle (Scheme 1b). Importantly, recent work has suggested the feasibility of such $Pd^{II/IV}$ catalysis in related directed C−H activation/C−C coupling reactions.[6,7] We report herein that this new oxidative approach successfully affords 2-arylindoles in high yields under unprecedentedly mild conditions.



(1)

Our initial studies focused on the phenylation of 1-methylindole with $[Ph-I-Ph]BF_4$ in the presence of 5 mol % of $Pd(OAc)_2$ (eq 1). We were pleased to discover that the desired 2-phenylated product **1a** was obtained in 49% yield, under extremely mild conditions—*within 5 min at room temperature*. In addition, this transformation showed no sensitivity to air and moisture and could be conveniently carried out on the benchtop using unpurified solvents. Interestingly, starting material **1** was not completely consumed under these conditions (with $Pd(OAc)_2$ as the catalyst); however, the use of longer reaction times and/or elevated temperatures did not afford increased yields, suggesting that catalyst deactivation might be occurring in this system. As such, we reasoned that Pd^{II} complexes containing more stabilizing ancillary ligands might result in improved performance, and a screen of

Scheme 1. $Pd^{0/II}$ versus Proposed $Pd^{II/IV}$ Mechanism for Indole Arylation



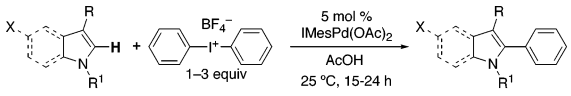
potential catalysts (see Table S1) revealed that $IMesPd(OAc)_2$ [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] afforded a significantly enhanced 86% isolated yield of **1a**. The $IMesPd(OAc)_2$-catalyzed reaction also proceeded at room temperature, but the rate slowed significantly with this more electron-rich Pd^{II} catalyst (requiring 18 h at 25 °C), consistent with a mechanism involving electrophilic palladation as a key step.[8]

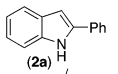
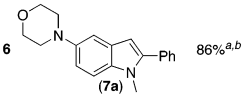
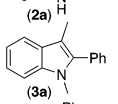
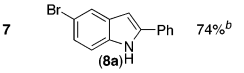
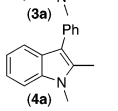
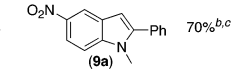
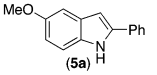
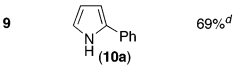
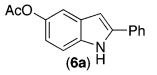
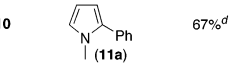
As summarized in Table 1, $IMesPd(OAc)_2$-catalyzed phenylation with $[Ph-I-Ph]BF_4$ could be extended to a variety of different indole substrates. *Most notably, free indoles exhibited comparable reactivity to N-methyl indoles in these transformations*; for example, reaction of indole provided **2a** in 81% isolated yield at room temperature, without competing *N*-arylation or other undesired side reactions (entry 1). In contrast, the $Pd^{0/II}$-catalyzed arylation of free indoles typically requires forcing conditions as well as the addition of strong bases (both to protect the nitrogen and to render the heterocycle more electron rich) in order to achieve comparable yields.[2] These transformations were also compatible with a diverse variety of electron-donating and -withdrawing substituents, including aromatic ethers, esters, amines, and nitro groups (entries 4, 5, 6, and 8). In addition, aryl bromides (entry 7) were well tolerated. The latter is particularly notable, as these serve as valuable functional handles for further manipulation of the products and often undergo side reactions during $Pd^{0/II}$ catalytic cycles. Finally, the arylation of pyrrole derivatives was also facile under comparable conditions (entries 9 and 10). Importantly, these oxidative arylations typically proceeded with very high (>20:1) selectivity for formation of 2-phenylated products. Appreciable amounts of phenylation at the more electrophilic C-3 position were only observed when C-2 was blocked (for example, in 1,2-dimethylindole, entry 3).[9] These results are consistent with a mechanism involving initial palladation at C-3 followed by fast Pd migration to C-2,[2a,4e,f] and detailed investigations are underway to gain further insights into this key palladation step.

We next turned our attention to the introduction of diverse Ar substituents onto the indole core. Initial investigations revealed that both the mesityl-substituted I^{III} reagents,[6a] $[Mes-I-Ar]BF_4$, as well as the symmetrical I^{III} compounds, $[Ar-I-Ar]BF_4$, afforded the desired 2-Ar-substituted indoles. In general, the latter resulted in superior conversions and yields with $IMesPd(OAc)_2$ as the catalyst. As shown in Table 2, a variety of electron-donating and electron-

10.1021/ja060809x CCC: $33.50

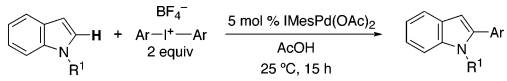
Table 1. Phenylation of Diverse Indoles and Pyrroles

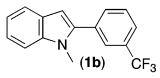
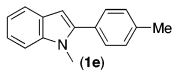
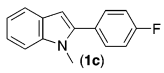
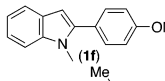
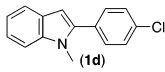
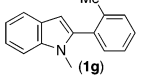
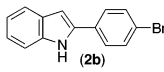
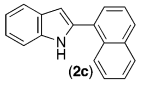


Entry	Product	Yield	Entry	Product	Yield
1	 (**2a**)	81%	6	 (**7a**)	86%[a,b]
2	 (**3a**)	89%	7	 (**8a**)	74%[b]
3	 (**4a**)	29%	8	 (**9a**)	70%[b,c]
4	 (**5a**)	58%	9	 (**10a**)	69%[d]
5	 (**6a**)	71%	10	 (**11a**)	67%[d]

[a] With 10 mol % catalyst. [b] At 60 °C. [c] With 6 equiv of $[Ph-I-Ph]BF_4$. [d] With 10 equiv of substrate relative to $[Ph-I-Ph]BF_4$.

Table 2. Introduction of Diverse Aryl Groups

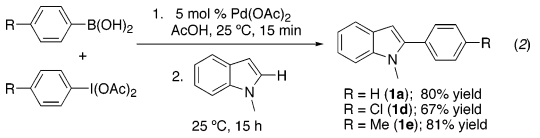


Entry	Product	Yield	Entry	Product	Yield
1	 (**1b**)	64%	6	 (**1e**)	70%
2	 (**1c**)	80%	7	 (**1f**)	80%[b]
3	 (**1d**)	90%	8	 (**1g**)	62%[b]
4	 (**2b**)	66%[a]	9	 (**2c**)	67%[b]

[a] Carried out at 80 °C due to low solubility $[Ar-I-Ar]BF_4$. [b] At 60 °C.

withdrawing aryl substituents as well as sterically hindered 1-naphthyl and *o*-methyl groups could be installed with these symmetrical arylating reagents, all with excellent (>20:1) selectivity for functionalization at C-2. In comparison, bulky *o*-substituted aryl groups typically result in only modest levels of C-2 selectivity in analogous $Pd^{0/II}$-catalyzed reactions.[2a]

A potential limitation for the widespread utility of this methodology is the requirement for the independent (albeit straightforward)[10] 1−2 step synthesis of the I^{III} arylating reagents. As such, we next sought to develop a practical one-pot approach to these transformations starting with $ArI(OAc)_2$[10a] and commercially available arylboronic acids. Initial studies revealed that combining $PhB(OH)_2$ and $PhI(OAc)_2$ in AcOH for 15 min at room temperature in the presence of 5 mol % of $Pd(OAc)_2$ followed by the addition of 1-methylindole resulted in the formation of **1a** in 80% isolated yield (eq 2). This simple procedure could be readily extended to the construction of other 2-arylated indole derivatives. For example, the combination of $Ar-I(OAc)_2$ (Ar = *p*-ClC_6H_4 or *p*-MeC_6H_4) with the corresponding arylboronic acid and $Pd(OAc)_2$ followed by the addition of 1-methylindole resulted in good yields of **1d** and **1e**.[11] The comparable yields and similarly mild reaction conditions required for these transformations relative to those with preformed $[Ar-I-Ar]BF_4$ suggest that analogous I^{III}-based arylating reagents are generated in situ in these systems.



In conclusion, this paper describes the rational development of a new Pd^{II}-catalyzed method for the direct 2-arylation of indoles. These reactions proceed under remarkably mild conditions (often at room temperature) and are compatible with ambient air/moisture—features that are proposed to be a consequence of a $Pd^{II/IV}$ pathway in these systems. The synthetic utility of these reactions is further enhanced by their high selectivity for arylation at C-2 and by the ability to generate active arylating reagents in situ from simple precursors. Ongoing work seeks to gain further insights into the mechanism of these reactions and to expand their scope to the arylation of unactivated arenes and alkanes.

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Note Added after ASAP Pulication. After this paper was published ASAP on March 24, 2006, new information was added to the Materials and Methods paragraph on page S1 of the Supporting Information, along with two new references on page S11. The updated Supporting Information was made available on March 29, 2006.

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

References

(1) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.
(2) For the $Pd^{0/II}$-catalyzed arylation of indoles, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (c) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (d) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148.
(3) For Rh-catalyzed arylation of NH indoles, see: Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.
(4) For Pd^{II}-catalyzed indole alkenylation/alkylation, see: (a) Jia, C.; Lu, W.; Kitamura, T. *Org. Lett.* **1999**, *1*, 2097. (b) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927. (c) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (d) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250. (e) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (f) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854.
(5) For recent examples of $Pd^{0/II}$-catalyzed intermolecular arylation of nitrogen heterocycles, see: (a) Review: Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (d) Gauthier, D. R.; Limanto, J.; Devine, P. N.; Desmond, R. A.; Szumigala, R. H.; Foster, B. S.; Volante, R. P. *J. Org. Chem.* **2005**, *70*, 5938. (e) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (f) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578.
(6) For C−H activation/arylation reactions proposed to involve a $Pd^{II/IV}$ mechanism, see: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154 and references therein.
(7) For the synthesis of $Ar-Pd^{IV}$ complexes using $[Ar_2I]^+$-based oxidants, see: Canty, A. J.; Patel, J.; Rodemann, T.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 3466.
(8) As noted by a reviewer, the increased steric environment about IMesPd(OAc)$_2$ relative to $Pd(OAc)_2$ likely also contributes to the slower rates observed with this catalyst.
(9) The modest yield of **4a** is due in part to the formation of high molecular weight byproducts in this reaction.
(10) (a) Synthesis of $ArI(OAc)_2$: McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299. (b) Synthesis of $[Ar-I-Ar]BF_4$ or $[Mes-I-Ar]BF_4$: Chen, D. W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804.
(11) These in situ reactions also proceed efficiently to form **1a**, **1d**, and **1e** (in 44, 39, and 62% GC yield) using $MesI(OAc)_2$ and $ArB(OH)_2$.

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