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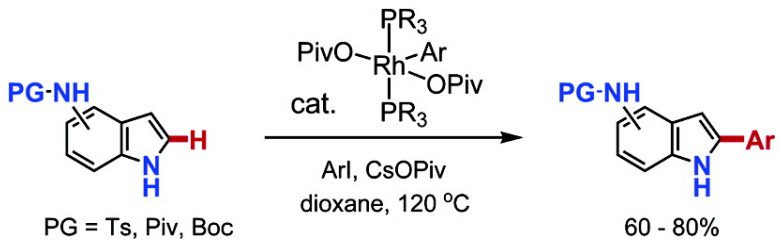

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Direct C-Arylation of Free (NH)-Indoles and Pyrroles Catalyzed by Ar−Rh(III) Complexes Assembled In Situ

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The direct C-arylation of free (NH)-azoles holds significant synthetic potential as it eliminates the need for introducing protecting groups and reactive functionalities prior to C−C formation, thereby enabling direct access to valuable heteroaromatic compounds. Such methods require selective targeting of C−H bonds in the presence of a reactive N−H functionality.[1] Faced with this challenge, we have recently employed azolylmagnesium or zinc salts as "protected" and "activated" substrates in a palladium (or cobalt)-catalyzed coupling with haloarenes (Scheme 1, route A).[2,3] However, due to the presence of the N−M moiety (M = Mg, Zn), this approach suffered from considerable moisture sensitivity and limited functional group scope.[4] Herein, we report an entirely different solution to this problem, which rests on the high reactivity and selectivity of aryl−rhodium(III) complexes, formed in situ, and allows direct arylation of free (NH)-indoles and pyrroles in the presence of a mild base (route B).

This project was initiated by uncovering an exciting lead; selective C-2 arylation of free indole was detected in the presence of $[Rh(coe)_2Cl]_2$ (coe = *cis*-cyclooctene), triphenylphosphine, and a weak base. On the basis of the assumption that this process proceeded via electrophilic metalation, we examined electron-deficient phosphines, which in turn led to the identification of $[p\text{-}(CF_3)C_6H_4]_3P$ as the best performing ligand. Subsequent optimization of other reaction parameters, notably, the base (see below) and the solvent, led to an efficient and selective catalytic system (Table 1, entry 1). Thus, the cross-coupling of indole and iodobenzene was achieved in the presence of $[Rh(coe)_2Cl_2]_2$ (**1**), $[p\text{-}(CF_3)C_6H_4]_3P$, and CsOPiv, furnishing 2-phenyl indole in 82% isolated yield with excellent regioselectivity (>50:1).

Next, we examined the functional group compatibility and substrate scope of this new system. Of particular interest were the protic functional groups, such as carbamate, carboxamide, and sulfonamide, which were problematic for the previous methods employing azolylmagnesium salts. This was due to the greater acidity of these groups in comparison to that of the indole amine (e.g., pK_a of sulfonamide ~ 13, azole amine ~ 21). Remarkably, these functionalities were well tolerated under the new catalytic conditions, affording the corresponding 2-phenyl derivatives as the principal products in good yield (Table 1, entries 3−5). This represents an important advance in the scope of the arylation methodology as *the new system targets C−H bonds exclusively in the presence of two acidic N−H bonds*!

Other common groups including halide, ketone, and ester were also compatible (see Supporting Information). A notable exception was 7-azaindole, which was completely inert under the reaction conditions (Table 1, entry 7). The inactivation by the basic sp^2 nitrogen represents a significant limitation of the present method and will be addressed in the future.[5] Otherwise, this protocol displayed low moisture sensitivity and allowed the direct use of commercial chemicals without further purification, benchtop handling, and gram scale experiments employing only 1 mol % of complex **1** (Table 1, entries 1 and 2).

Scheme 1. A New Approach to C-Arylation of (NH)-Azoles (route B)

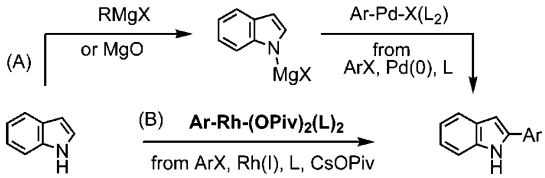
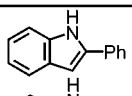
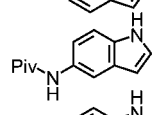
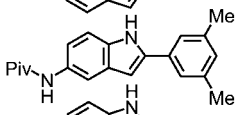
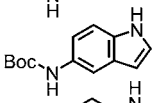
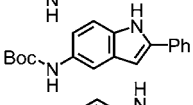
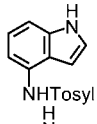
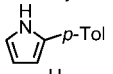
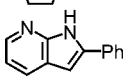


Table 1. Substrate and Functional Group Scope[a]

Entry	Azole	Product	Isolated Yield
1			82%
2			75%[b]
3			78%
4			59%
5			65%
6			81%
7			0%

[a] For complete list of substrates (15 examples), see Supporting Information. Reaction conditions: 1 equiv of azole, ArI (1.2 equiv), CsOPiv (1.4 equiv), **1** (2.5 mol %), L (15 mol %). Dioxane/120 °C/18−36 h. [b] Indole (1.17 g), **1** (1 mol %), L (6 mol %), all reagents weighed in air, 120 °C/56 h. L= $[p\text{-}(CF_3)\text{-}C_6H_4]_3$ P.

In the course of our investigation, the key importance of the base was noted as only cesium carboxylates gave appreciable yields (carbonates and phosphates of alkali metals as well as amines were ineffective); CsOPiv clearly stood out as the base of choice (CsOAc versus CsOPiv, 45 versus 82% yield). These observations led us to examine the mechanism, including the role of pivalate, in more detail. The ^{31}P NMR of the catalytic reaction mixture revealed a single observable Rh−phosphine species (δ 25.2 ppm, d, J_{Rh-P} = 113 Hz), which was later isolated and characterized as $Rh(OPiv)_2(Ph)L_2$ {**2**, L = $[p\text{-}(CF_3)C_6H_4]_3P$}. Complex **2** was also synthesized independently on a preparative scale in 89% yield from $[Rh(coe)_2Cl_2]_2$, the phosphine ligand, iodobenzene, and CsOPiv (Figure 1A). Thus, ligation of rhodium(I) by the phosphine, oxidative addition of iodobenzene, and displacement of the halides by pivalate at the Rh(III) center describes the likely course of events. Owing to unfavorable solubility properties of **2**, its tolyl analogue, $Rh(OPiv)_2(4\text{-tolyl})L_2$ (**3**), was prepared in a similar manner (55%

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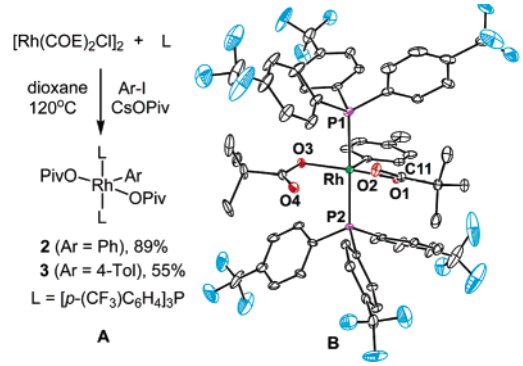
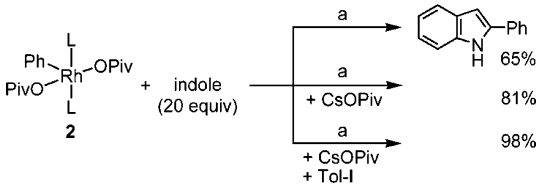


Figure 1. (A) Synthesis of **2** and **3**. (B) X-ray structure of **3** (ORTEP).

Scheme 2. Reactivity of Complex **2**[a]



[a] L = [*p*-(CF$_3$)C$_6$H$_4$]$_3$P, 4-Tol = *p*-(CH$_3$)C$_6$H$_4$. Conditions: **2** (25 mM), dioxane, L (1 equiv), 120 °C, 120 min.

yield), and this complex yielded to crystallographic analysis. Complex **3**, in the solid state, is a five-coordinate rhodium species, containing two monodentate pivalate ligands (Figure 1). The ORTEP diagram revealed a surprising square pyramidal structure with five atoms (P1, P2, O1, O3, and Rh) forming the base plane.

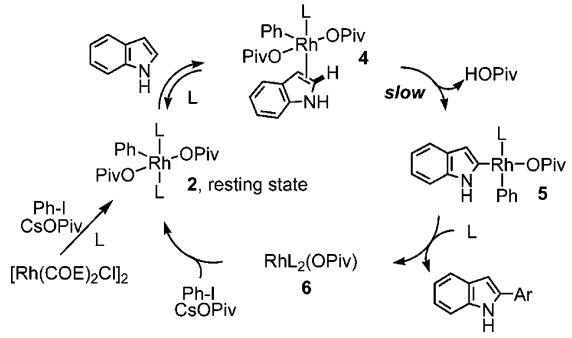
Rhodium complex **2** proved to be a competent catalyst, identical to the [Rh(COE)$_2$Cl]/[*p*-(CF$_3$)C$_6$H$_4$]$_3$P system in terms of rate and chemical yield. In stoichiometric experiments (in the absence of PhI and CsOPiv), complex **2** reacted with indole at 120 °C to furnish 2-phenyl indole in 65% yield (Scheme 2). This reaction displayed well-behaved initial rate kinetics (Supporting Information) and was determined to be *first order in complex **2** and indole, inverse first order in **L**, and zero order in PhI*. Although the yield of this reaction could be improved by the addition of CsOPiv and 4-Tol-I, the initial rate was not affected by these reagents. Thus, it seems that both CsOPiv and 4-Tol-I serve as trapping reagents,[6] preventing decomposition of the Rh(I) fragment formed in the reaction, instead of directly participating in the C−H bond functionalization.

These results are consistent with the following overall structure of the catalytic cycle. Complex **2** is assembled in situ and represents the resting state of the catalyst. Subsequently, displacement of the phosphine ligand by indole takes place in a pre-equilibrium to form complex **4**, which is followed by the slow C−H bond metalation step (Scheme 3). The resulting intermediate **5** then undergoes reductive elimination, furnishing the desired coupling product. The rhodium(I) complex formed in this step is rapidly converted back to the resting state via oxidative addition of iodobenzene and halide−pivalate exchange. Thus, in brief, the oxidative addition of haloarene precedes the slow C−H transformation step.[7,8]

This model is further supported by the large kinetic isotope effect (k_H/k_D = 3.0) at the 2-position of indole. Although the intimate mechanistic details of the C−H metalation step are unclear, we propose that the pivalate ligand assists the C−H bond dissociation as an internal base. This is consistent with the fact that the initial rates of the reaction between indole and complex **2** were not affected by the addition of CsOPiv.[9,10]

In summary, we describe a novel system for direct C-arylation of free (NH)-indoles and pyrroles, with tolerance for a wide range

Scheme 3. Proposed Catalytic Cycle[a]



[a] L = [*p*-(CF$_3$)C$_6$H$_4$]$_3$P.

of functional groups, including those with acidic NH bonds. We propose that this remarkable selectivity stems from a greater electrophilicity of the Ar−Rh(III) fragment [as compared to Ar−Pd(II)], further augmented by the "electron-deficient" phosphine and the pivalate ligand, which translates to higher reactivity of this intermediate and, consequently, milder reaction conditions. In stark contrast to N-metalation and activation of the azole substrate by magnesium or zinc bases, CsOPiv activates the rhodium catalyst by providing the required pivalate ligand, which in turn plays an important role in the key C−H metalation step.

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Supporting Information Available: Experimental procedures, spectral data, crystallographic data for **3** (CIF), kinetics of stoichiometric and catalytic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) N-arylation is well established. For lead references, see: (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.
(2) (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (b) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607.
(3) For work of others, see: Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981.
(4) These methods require rigorously anhydrous conditions (solvent, glassware) and very pure azole substrates.
(5) For the same reason, imidazole and pyrazole were inert. For a complete list of substrates, see Supporting Information.
(6) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937.
(7) It should be noted that this mechanism differs significantly from that proposed for the rhodium-catalyzed arylation of benzimidazole and benzoxazole at the 2-position (electron-deficient position), wherein C−H bond activation takes place first, generating a Rh(I)−carbene complex, followed by the oxidative addition of iodobenzene. Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35.
(8) No mechanistic data have been generated for Rh-catalyzed directed ortho-arylation: (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669.
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