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# Selective C-Arylation of Free (NH)-Heteroarenes via Catalytic C−H Bond Functionalization

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Heteroaromatics are important structural units frequently found in natural products, pharmaceuticals, and other functional synthetics. The direct arylation of a heterocyclic core would eliminate the need for establishing a reactive functionality (cf., halogenation or stoichiometric metalation) prior to C−C coupling, enabling direct elaboration and expansion of the core motif. We have recently developed palladium-catalyzed arylation of alkane segments in complex substrates.[1] This work led us to explore the arylation of C−H bonds in a broad spectrum of organic substrates, including heteroarenes.

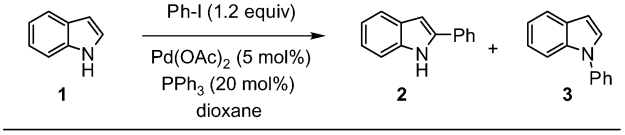
The palladium-catalyzed arylation of oxazole, thiazole, and protected azoles (pyrrole, indole, and imidazole) has been reported with aryl halides in the presence of a base.[2] However, these reactions often suffered from low yields and poor selectivity.[3] Furthermore, in the course of our investigations, we found that free pyrrole, indole, and imidazole were unreactive under known arylation conditions, yielding little or no C-arylation products (Table 1).

Thus, we set out to explore the possibility of selective C-arylation of free (NH)-azoles, a challenge attainable through selective targeting of C−H bonds in the presence of free N−H functionality. We initially proposed that formation of a salt possessing a strong metal−nitrogen bond may not only protect the amino function, but also increase nucleophilicity of the annular carbon centers of the heteroarene. This simple hypothesis guided our search for a suitable metal base (Table 1). As it turned out, standard alkali metal bases failed completely, including the best performing base for the arylation of oxazole and thiazole, $Cs_2CO_3$.[2] *To our delight, we found that MgO afforded compound* ***2*** *as a single product in 53% yield (unoptimized).* It is noteworthy that no N-arylation product was detected in the crude mixture and also that arylation occurred exclusively at position 2 of the indole. This finding reminded us of the classical indole Grignard salts, which are known to provide a higher degree of C-alkylation in comparison to alkali salts.[4] Indeed, indole Grignard salt **4**, prepared from indole and EtMgBr, furnished product **2** exclusively in 65% yield. As judged by $^1$H and $^{13}$C NMR, a species similar to indolylmagnesium bromide, presumably magnesium hydroxide salt **5**, was formed from indole and MgO. MgO is a convenient and practical base because of its low cost and ease of handling (benchtop handling).

After some optimization (solvent, temperature), 2-phenylindole **2** was prepared as the exclusive product in 84% yield by the coupling of indole and iodobenzene (Figure 1). This new method was compatible with both electron-donating and electron-withdrawing groups in the para position of iodobenzene. In contrast, 2-iodotoluene underwent slower reaction, affording two products, 2-arylation product **11** (39%) and 3-arylation product **12** (12%). The yields were improved by addition of an excess of 2-iodotoluene (2.5 equiv), yielding **11** and **12** in 55% and 17% yield, respectively. At present, we may only speculate on the factors determining the regiochemical course of this reaction. Presumably, the arylation of indole may occur via two mechanistic modes: (1) electrophilic metalation with Ph−Pd−X, followed by reductive elimination, or (2) carbopalladation of the double bond, followed by anti-elimination of hydrogen palladium species.[5] Because C-3 of the indole magnesium salt is expected to be more nucleophilic than C-2, the latter mechanism may explain the formation of 2-arylation products. However, it is also plausible that the metalation step prefers the C−H bond adjacent to the nitrogen atom. Similar trends have been observed with protected indole substrates.[2]

We then continued to test the applicability of this methodology to other (NH)-heteroarenes, including pyrrole, pyrazole, and imidazole. In each case, a single C-arylation product was isolated in good to excellent yield; neither N-arylation nor bis-arylation products were detected under the conditions employed (Table 2).[6] Specifically, pyrrole afforded 2-phenylpyrrole in 86% yield, pyrazole gave 3-phenylpyrazole in 81% yield, and 2-phenylimidazole furnished 2,4-diphenylimidazole in 81% yield. Remarkably, free imidazole also furnished a single product in 72% yield, which was identified as 4-phenylimidazole (Table 2, entry 4). The selectivity observed with pyrrole (C-2) and imidazole (C-4) is consistent with an electrophilic substitution mechanism. However, in the case of

***Table 1.*** Metalation as N-Protection and Activation of Heteroarenes[a]




| 4, X=Br / 5, X=OH | BASE (1.2 equiv) | isolated yield (**2** / **3**) |
|---|---|---|
| | LiOH or NaOMe | 0 / 0 % |
| | $K_3PO_4$ or KOAc | 0 / 0 % |
| | $Cs_2CO_3$ | 0 / 5% |
| | **MgO** | **53 / 0%** |
| | **EtMgBr[a]** | **65 / 0%** |
| | ZnO | 44 / 0% |

[a] Conditions: 150 °C, 15 h. (a) Indolyl Grignard salt **4** was prepared prior to the arylation reaction.

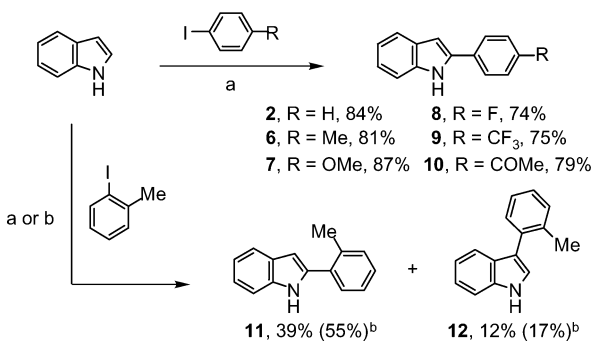



***Figure 1.*** Scope of free indole arylation. Conditions: (a) Ar−I (1.2 equiv), $Pd(OAc)_2$ (5 mol %), $PPh_3$ (20 mol %), MgO (1.2 equiv), dioxane/DMF (1:2), 150 °C, 18 h. (b) 2.5 equiv of 2-Me$C_6H_4$−I.



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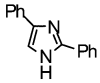
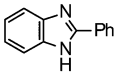
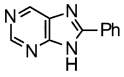
***Table 2.*** Highly Selective C-Arylation of Free (NH)-Azoles[a]

| entry | substrate | condition | product | yield |
|---|---|---|---|---|
| 1 |  | Ph-I (1.2 equiv), a |  | 86% |
| 2 |  | a |  | 81% |
| 3 |  | a |  | 81% |
| 4 |  | a |  | 72% |
| 5 |  | a + CuI (2 equiv) |  | 83% |
| 6 |  | a + CuI (0.2 equiv) |  | 90% |
| 7 |  | a + CuI (0.2 equiv) |  | 78% |

[a] Conditions: (a) PhI (1.2 equiv), $Pd(OAc)_2$ (5 mol %), $PPh_3$ (20 mol %), MgO (1.2 equiv), dioxane, 150 °C, 12−15 h. PhBr afforded 52−60% yield of the corresponding products.

pyrazole, C-3 arylation stands in contrast to electrophilic substitution reactions which occur at C-4. As in the indole case (see discussion above), either the addition−elimination mechanism or the activating effect of the neighboring nitrogen on the metalation step may be responsible for the observed "nucleophilic" selectivity.[7]

The selectivity obtained in the arylation of free imidazole prompted us to explore whether the *regio*-course of this reaction could be altered. We considered Cu(I) salts as a potential cocatalyst/additive because of their ability to catalyze arylation of active methylene and methine groups.[8] However, the issue of C- versus N-arylation emerged again in this context as copper salts have also been shown to catalyze the selective N-arylation of heterocycles.[9,10] To our great delight, addition of CuI to the new $Pd/Ph_3P/MgO$ system resulted in exclusive arylation of position 2 in 83% yield. Hence, a complete switch from 4-arylation to 2-arylation of imidazole was brought about by a simple alteration of the arylation protocol (entries 4 and 5, Table 2). Furthermore, efficient arylation of benzimidazole and purine was demonstrated, furnishing high yields of the anticipated monoarylation products (Table 2).

These new results raise many interesting mechanistic questions regarding the selectivity of these orthogonal methods. Certainly, the selective arylation of C−H bonds may be attributed to the formation of magnesium salts [cf., (XMg−N)-azole] in the presence of MgO. We reason that the strong magnesium−nitrogen bond not only protects the nitrogen from attack by other electrophiles [in this instance, Ph−Pd−$X(L_2)$] but also increases the nucleophilicity of the heteroarene nucleus. In contrast, alkali ions, preferring the solvation sphere, release the azolyl anion which in turn inhibits the palladium catalyst. This scenario provides a rationale for low reactivity of free (NH)-azoles under arylation conditions employing standard alkali bases.[11] However, in the presence of an appropriate ligand (e.g., DPPF, $tBu_3P$, 2-biaryl-dialkylphosphine, N-heterocyclic carbene ligands), the azolyl anion is able to undergo N-arylation.[6]

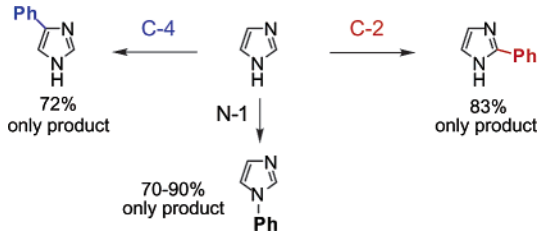



***Figure 2.*** Arylation of imidazole. Complete orthogonality.

Imidazole represents a substrate that best illustrated the remarkable selectivity of the methodology developed herein (Figure 2). In fact, we have found that imidazole may be functionalized with *complete chemo- and regiocontrol* via fully orthogonal arylation methods. These novel C-arylation methods described herein serve to complement the selective N-arylation developed previously by other groups.[9,10]

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**Supporting Information Available:** Experimental procedures, spectral data for all products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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