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Direct C–H Bond Arylation: Selective Palladium-Catalyzed C2-Arylation of *N*-Substituted Indoles

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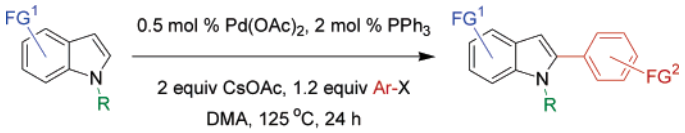
ABSTRACT



R = alkyl or aryl; FG = functional group

We present a new, practical method by which *N*-substituted indoles may be selectively arylated in the C2-position with good yields, low catalyst loadings, and a high degree of functional group tolerance. Our investigation found that two competitive processes, namely, the desired cross-coupling and biphenyl formation, were operative in this reaction. A simple kinetic model was formulated that proved to be instructive and provided useful guidelines for reaction optimization; the approach described within may prove to be useful in other catalytic cross-coupling processes.

Indoles represent important structural units frequently found in natural products, pharmaceuticals, and other synthetics. Current methods for C2-arylation of *N*-substituted indoles require functionalization of the heteroarene substrate, i.e., synthesis of the corresponding stannane or boronate, prior to a palladium-catalyzed C−C coupling.[1] However, there is little precedent for the *direct intermolecular reaction* of *N*-substituted indoles with aryl halides currently limited to low-yielding reactions with specialized chloropyrazine donors.[2] In this context, we came to appreciate that indoles were significantly less reactive in comparison to other five-membered heteroarenes. Consequently, we directed our attention to this problem and found critical roles for the base and catalyst loading in these coupling reactions. As a result, we herein present a new, practical method by which (*N*-R)-indoles may be arylated in the C2-position selectively in good to excellent yields, with low catalyst loadings and a high degree of functional group tolerance.

Our initial investigations demonstrated that the standard conditions developed for palladium-catalyzed arylation of five-membered heteroarenes were not suitable for (*N*-R)-indole substrates. These conditions often used carbonate or acetate bases at higher temperatures as well as relatively high catalyst loadings (entry 3 and 4, Table 1).[3] Furthermore, in contrast to furan, pyrrole, oxazole, and related systems, indole arylation does not follow the "electrophilic" regiochemistry but instead shows high C-2 selectivity.[4] We also examined the conditions recently developed in our group for the arylation of free (*N*-H)-heteroarenes (Table 1, entry 1).[5] It became apparent that MgO was not a suitable base for (*N*-R)-indole substrates, confirming the importance of the magnesium salt (*N*-MgX) formation in the case of free

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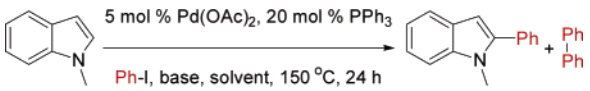
Table 1. Critical Role of Base in the Indole C2−Arylation Reactions[a]



			yield %	
entry	base	solvent	product	biphenyl
1	MgO	dioxane/DMF (1:2)	3	12
2	ZnO	dioxane/DMF (1:2)	8	24
3	CS_2CO_3	DMA	21	28
4	KOAc	DMA	27	34
5	**CsOAc**	**DMA**	**48**	**28**
6	CsOTFA	DMA	11	37

[a] All yields were determined by HPLC versus an internal standard. For complete data, see Supporting Information.

indoles. A significant improvement was accomplished via a systematic investigation of the base, which ultimately led us choose cesium acetate as the optimum reagent (Table 1, entry 5). Although the importance of the carboxylate ion/ligand in the palladation of both sp^3 and sp^2 C−H bonds has been recognized,[6] in this case both the cation and anion play an essential role.[7] For example, both potassium acetate and cesium trifluoroacetate provided low amounts of the product (Table 1, entries 4 and 6, respectively).[8] However, even with CsOAc the reaction efficiency was low, affording 48% yield of the desired product as well as 28% yield of biphenyl. It became clear that *biphenyl formation represented a key competitive process responsible for consuming the iodobenzene before full conversion of the substrate could occur*.

The palladium-catalyzed Ullmann coupling is a well-established protocol;[9] moreover, it represents a frequently encountered problem in hetero cross-coupling reactions such as the Heck reaction and related processes.[10] Surprisingly, this issue has not been previously addressed in this context, and thus there are no general guidelines available to mitigate biphenyl byproduct formation. Consequently, we proposed a qualitative kinetic model of the reaction system presented here, which in turn guided our optimization studies (Figure 1).

We surmised that the first step, namely, oxidative addition, proceeds to an aryl-palladium halide intermediate, which may

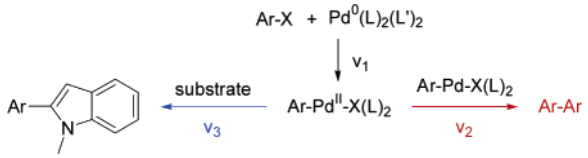


Figure 1. Proposed kinetic model of the reaction system.

then undergo two competing pathways: (1) cross-coupling with the substrate to furnish the desired product or (2) formation of byproduct biphenyl. Although the mechanistic details of these processes have not been elucidated,[5] we made an informed assumption that biphenyl formation required a bimolecular transmetalation of the aryl-palladium species (Figure 1).[11]

Despite its simplicity, this model predicts several features of significant practical consequence. For instance, *decreasing the catalyst loading should increase the rate ratio v_3/v_2 and thus favor production of the desired product.* To test this hypothesis, arylation of *N*-methylindole with iodobenzene was conducted over a range of catalyst loading; in these experiments, the concentration of the substrate was kept constant (Figure 2). Indeed, decreasing the amount of catalyst

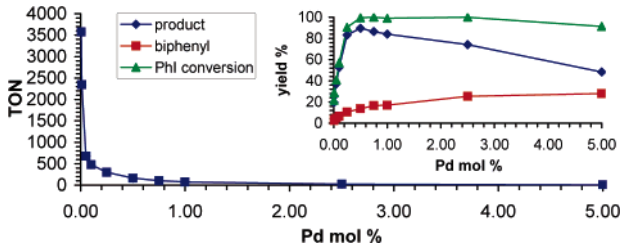


Figure 2. Chemical yield and TON as a function of catalyst loading in reaction of *N*-methylindole and Ph-I: $Pd(OAc)_2/PPh_3$ (1:4), 2.54 M in substrate, CsOAc, DMA, 125 °C, 24 h.

(starting from 5 mol % Pd) led to a steady increase of the product yield at the expense of biphenyl formation, reaching a maximum at 0.5 mol % Pd (Figure 2). The inverse relationship between the catalyst loading and the chemical yield is highly desirable, particularly at the lower range of catalyst loading as observed herein.[12]

Lowering the catalyst amount below 0.5 mol % led to a sharp decline in yield, which was accompanied by a dramatic increase in the catalyst turnover number (Figure 2). At such low concentrations, catalyst decomposition processes, including biphenyl formation were suppressed. However, the reaction rates were too slow to afford practical yields within

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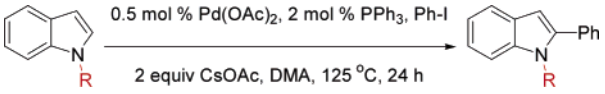
a reasonable reaction time. The same trends were observed when the substrate concentration was decreased 10-fold from 2.54 to 0.254 M. Virtually identical yields for both 2-phenyl-1-methylindole and biphenyl were obtained at the two different concentrations.[13] These experiments demonstrated that the substrate/catalyst ratio (and not the absolute concentration) determine the yield and product distribution, lending further support for the kinetic model introduced earlier.

As a result of this exercise, the protocol requiring only 0.5 mol % catalyst (optimized for the parent coupling partners) was subsequently applied to a broad range of substrates in order to investigate the substrate scope.

First, we investigated the scope of *N*-substitution on the indole nucleus (Table 2). Both *N*-alkyl and *N*-arylindoles

Table 2. Reaction Scope: Substitution at Nitrogen



entry	R	yield %[a]	entry	R	yield %[a]
1	CH_3	88 (54)[b]	4	Ph	68
2	Bn	81	5	*p*-(CN)-C_6H_4	55
3	*i*Pr	92	6	SO_2Ph, SO_2CH_3, $COCH_3$	0

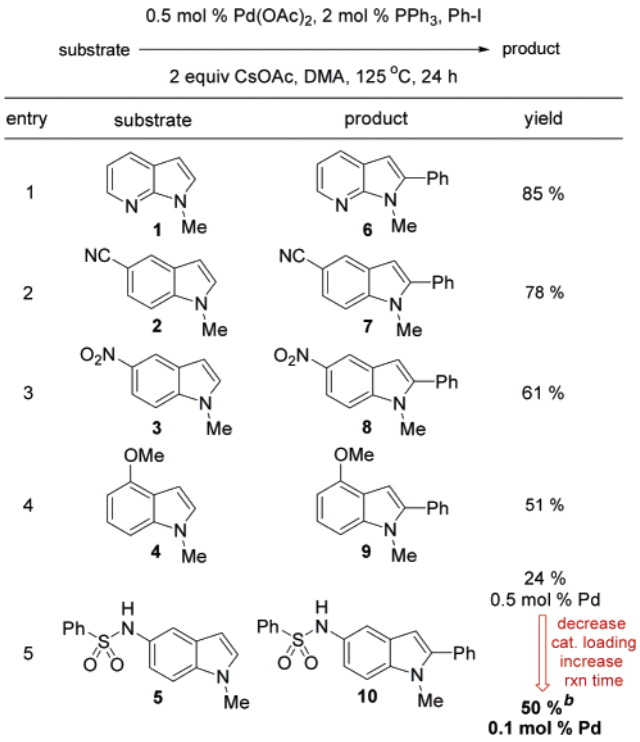
[a] All values based on isolated yields. [b] Chlorobenzene was used as donor and dicyclohexylphenylphosphine as a ligand at 150 °C.

proved to be suitable substrates, while *N*-sulfonyl or *N*-acetylindole were inert. These results clearly indicated the need for sufficient electron density on the pyrrole ring to facilitate substitution.

Subsequently, we examined more complex substrates bearing various substituents on both the indole and the haloarene components (Tables 3 and 5). To our delight, many functional groups were well tolerated in these reactions. The modest yields observed in some cases may be ascribed to two main factors: (1) the low stability of the substrate and the corresponding product (cf. entries 3 and 4, Table 3) or (2) the low reactivity of the substrate. The latter case may be illustrated by 5-sulfonamido-1-methylindole **5**, a slow yet stable substrate, which furnished only a 31% yield of product **10** and a 10% yield of biphenyl (Table 4). In such instances, the kinetic model discussed above (Figure 1) may once again prove to be instructive. The slow v_3 rate will favor biphenyl formation and unproductive consumption of iodobenzene. In resonance with this analysis, increasing the reaction time from 24 to 48 h led only to a minor improvement in the yield of product **10** (31→34%), while the yield of biphenyl was doubled (10→22%), Table 4. According to our model, this should be correctable by further lowering the catalyst concentration. Indeed, this proved to be the case, as decreasing the loading from 0.5 to 0.1 mol % $Pd(OAc)_2$ resulted in a significant increase in the production of **10** at the expense of biphenyl formation (Table 4). In practical terms, decreasing the catalyst load and increasing the reaction time to compensate for a slower product formation afforded a 2-fold enhancement of the isolated yield of **10** (24→50%, Table 3).

(13) See Supporting Information for data.

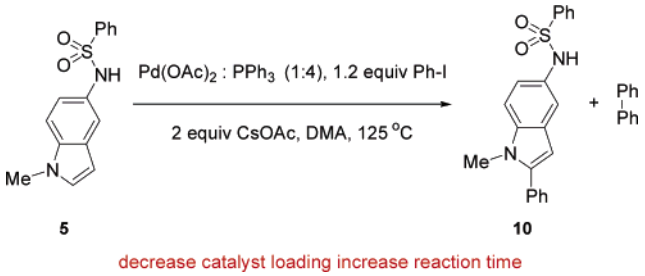
Table 3. Reaction Scope: Substitution on Indole[a]



[a] All values based on isolated yields; conditions were the same as in Table 2. [b] Performed with 0.1 mol % $Pd(OAc)_2$, 0.4 mol % PPh_3; reaction time was 48 h.

C2-arylation was generally preferred unless the haloarene donor contained a substituent in the *ortho*-position. In these circumstances, a mixture of C2- and C3-arylation products was obtained. Since biphenyl homocoupling is not an issue

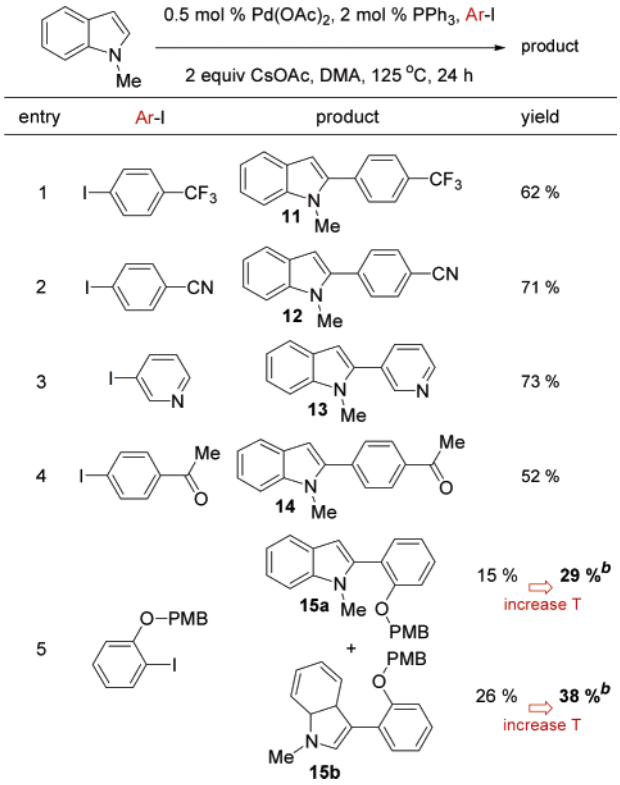
Table 4. Optimization of Substrates with Slow v_3[a]



			yield %	
entry	time (h)	mol % $Pd(OAc)_2$	product	biphenyl
1	24	0.5	31	10
2	48	0.5	34	22
3	48	0.1	52	13

[a] All values based on HPLC yields versus an internal standard.

Table 5. Reaction Scope: Substitution on Arene Donor



[a] All values based on isolated yields; conditions were the same as in Table 2. [b] Performed at 150 °C.

with these particular donors (v_2 is very slow), the desired cross-coupling yield could in fact be improved by increasing the reaction temperature, provided the substrates and products are sufficiently stable (cf. **15**, 41→67% combined yield, Table 5).

Last, it is notable that similar reactivity trends were found employing chlorobenzene in place of Ph-I, although the chemical yields were lower (cf. 54% with *N*-methylindole, Table 2, entry 1). Future studies will address the use of other haloarene donors.

In conclusion, a practical new, method has been developed for the selective C2-arylation of *N*-substituted indoles. Careful evaluation of the reaction conditions identified the base and the catalyst loading as two key factors. Reducing the catalyst loading suppressed the formation of biphenyl byproduct and enhanced product formation. Good functional group tolerance was demonstrated, and a simple kinetic model was used to guide optimization of complex indole substrate arylation. We believe that this kinetic model may prove to be valuable for optimization of other cross-coupling reactions.

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Supporting Information Available: Experimental procedures, spectral data, base optimization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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