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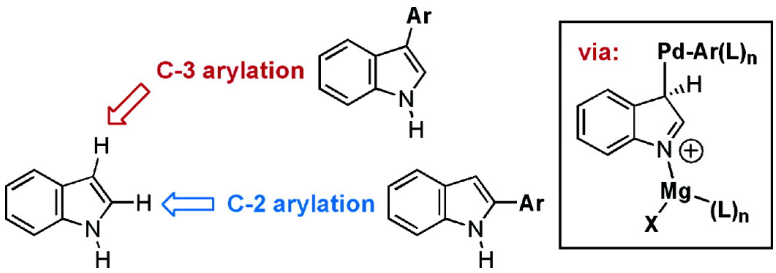

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Direct Palladium-Catalyzed C-2 and C-3 Arylation of Indoles: A Mechanistic Rationale for Regioselectivity

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Abstract: We have recently developed palladium-catalyzed methods for direct arylation of indoles (and other azoles) wherein high C-2 selectivity was observed for both free (NH)-indole and (NR)-indole. To provide a rationale for the observed selectivity ("nonelectrophilic" regioselectivity), mechanistic studies were conducted, using the phenylation of 1-methylindole as a model system. The reaction order was determined for iodobenzene (zero order), indole (first order), and the catalyst (first order). These kinetic studies, together with the Hammett plot, provided a strong support for the electrophilic palladation pathway. In addition, the kinetic isotope effect ($KIE^{H/D}$) was determined for both C-2 and C-3 positions. A surprisingly large value of 1.6 was found for the C-3 position where the substitution does not occur (secondary KIE), while a smaller value of 1.2 was found at C-2 (apparent primary KIE). On the basis of these findings, a mechanistic interpretation is presented that features an electrophilic palladation of indole, accompanied by a 1,2-migration of an intermediate palladium species. This paradigm was used to design new catalytic conditions for the C-3 arylation of indole. In case of free (NH)-indole, regioselectivity of the arylation reaction (C-2 versus C-3) was achieved by the choice of magnesium base.

Introduction

Direct C−H Functionalization in Heteroarenes: Selective C-Arylation of Indole. Azoles represent important structural units frequently found in natural products, pharmaceuticals, and other synthetics. Direct arylation of heteroarenes, achieved via cross-coupling of (sp^2) C−H bonds and haloarenes,[1] offers an attractive alternative to standard cross-coupling methods which require the establishment of a reactive functionality prior to C−C coupling (i.e., halogenation, metalation).[2] It has been our aim to develop parallel methodologies capable of furnishing regioisomeric products from the same substrate, governed by the catalytic system employed (Figure 1).[3] In this regard, indole represents a system of particular interest and importance. The C-2 and C-3 selective methods would be valuable and complementary to the known N-arylation methodology,[4] enabling the direct access to a series of indole derivatives (Figure 1). In this paper, we describe the experimental studies that not only provided a mechanistic rationale for the C-2 arylation reaction but also led to the development of new conditions for C-3 selective arylation of free (NH)-indoles.

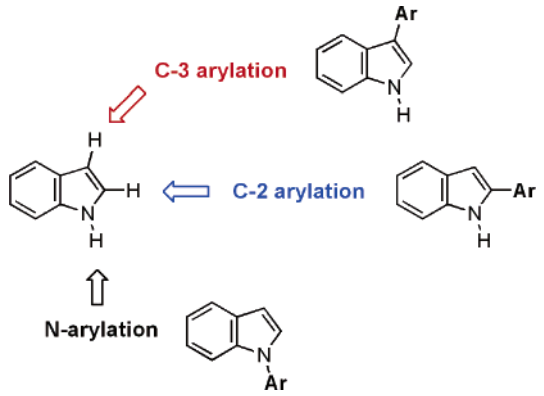

Figure 1. Direct and systematic arylation of indole. Regioselectivity control.

C2-Arylation of Indoles: Effect of N-Substitution. We have previously reported selective C-arylation of free (NH)-azole heteroarenes (Scheme 1).[3] This method was also effective for indole substrates, affording C-2 arylation products. The pivotal step in this process involves the in situ formation of an indole magnesium salt (*N*-MgX) in the presence of MgO, which not only protects the amine functionality but also increases the nucleophilicity of the azole ring (care must be taken with regard to the purity of indole and anhydrous conditions).[5] This new C-arylation protocol ($Pd/Ph_3P/MgO$) was highly regioselective; however, the observed trends were not uniform. Pyrrole and imidazole afforded products consistent with an electrophilic substitution mechanism,[6,7] while indole provided products

(1) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−41 and references therein.
(2) Labadie, S. S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250−4.
(3) (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580−10585. (b) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274−5275.
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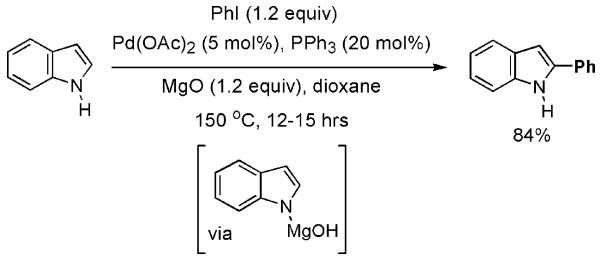
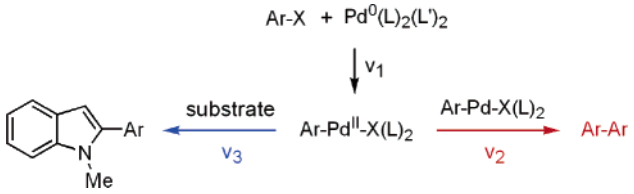
(5) See Supporting Information for a detailed and updated experimental procedure.

10.1021/ja043273t CCC: $30.25

Scheme 1. Selective C-2 Arylation of (NH)-Indole via in Situ Formation of Indole Magnesium Salts



Scheme 2. The Key Reaction Pathways in the C-2 Arylation of 1-Methylindole

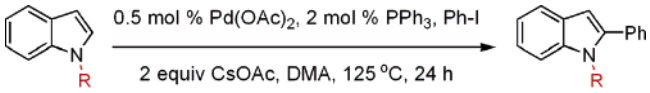


stemming from phenylation at the α-position to the nitrogen atom ("nonelectrophilic" regiochemistry, Scheme 1). To investigate the basis of the observed regioselectivity, we first examined whether the magnesium metal plays an important role in determining the regiochemical outcome. For this purpose, *N*-methylindole was selected as a model substrate.

This new 1-methylindole substrate required a full-scale optimization effort, which led to addressing two key issues: (1) the choice of base, and (2) formation of the biphenyl side product.[8] The first issue was solved when we found CsOAc to be an effective base, while MgO was ineffective, lending further support for its role in the free indole arylation. The second problem, the formation of biphenyl, was marginalized by decreasing the palladium catalyst loading. The entire reaction system can be described by a qualitative kinetic model shown in Scheme 2. The first step, oxidative addition between palladium(0) and the aryl-halide, proceeds to an aryl-palladium-(II) intermediate which is partitioned between two major competing pathways: (1) cross-coupling with the substrate to furnish the desired product or (2) formation of byproduct biphenyl. Despite its simplicity, this model suggested that the formation of the major side product, biphenyl, may be diminished by simply decreasing the amount of catalyst.[8] This favorable adjustment was inspired by an informed assumption that the biphenyl formation proceeds via a bimolecular transmetalation of the aryl-palladium species (Scheme 2).

Importantly, both the indole magnesium salt (Scheme 1) and the 1-alkylindole (Table 1) showed a strong preference for C-2 arylation, validating the latter as a suitable model substrate for the subsequent mechanistic studies. The resulting robust protocol required low catalyst loading (<0.5 mol % of Pd) and was compatible with a broad array of functional groups.[8] The effect of N-substitution is pertinent to the discussion below and deserves a note. N-Alkyl substituents including larger groups such as iso-propyl or benzyl as well as N-aryl groups were well tolerated, giving high yields of the corresponding 2-phenyl products (Table 1). In contrast, *N*-acetyl- and *N*-methansulfonyl-indole were completely inert, clearly indicating the need for high electron density in the azole-ring. In this paper, we provide a new mechanistic insight for the productive pathway, the reaction between the aryl-palladium(II) intermediate and indole (Scheme 2).

Table 1. . C-2 Arylation of (NR)-Indoles (Substitution on 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	Pr	92	6	SO_2Ph, SO_2CH_3, $COCH_3$	0

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

Results and Discussion

The Reaction Order of Iodobenzene, Indole, and the Catalyst. According to Scheme 2, the first step of the catalytic cycle involves formation of an aryl-palladium(II) intermediate via the oxidative addition of iodobenzene to a Pd(0) species. The reaction rate for the phenylation of 1-methylindole was measured over a range of iodobenzene concentrations (Supporting Information). These kinetic experiments determined that the reaction is zero order in iodobenzene, indicating that the rate-determining step occurs after the oxidative addition, most likely within the indole-functionalization sequence. Indeed, the reaction was first order in both indole and catalyst (see Supporting Information). This represents a favorable scenario as kinetic isotope experiments may shed more light on the mechanism of the C−H bond functionalization.

Alternative Mechanistic Pathways. There are three reaction mechanisms that may rationalize the strong preference for C-2 arylation of indole: (1) the electrophilic metalation-migration, (2) nonelectrophilic metalation of the 2-position, and (3) carbometalation, that is, Heck-type reaction (Scheme 3). The electrophilic substitution of the indole ring is well established, and a strong preference for the 3-position is known.[9] Thus, a C3 → C2 migration (1,2-migration) of palladium has to take place if this mechanism is operative. Alternatively, the direct C2-palladation of indole via a nonelectrophilic pathway (e.g., via σ-bond metathesis) would also explain the observed regioselectivity. C-2 palladation of indole has been reported; however, the presence of a strong directing group was required [cf., palladation of 1-(2′-pyridyl)-indole].[10] The carbo-metalation or the Heck-type reaction is also feasible; however, this pathway requires *anti*-dehydropalladation (or *anti*-β-hydride elimination).[11] To gain deeper insight into the mechanism of this

(6) Palladium-catalyzed arylation of other electron-sufficient heteroarenes afforded the "electrophilic regioselectivity". (a) Ohta, A.; Akita, A.; Ohkuwa, T.; Chiba, M.; Funkunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951−1958. (b) Sommai, P.-A.; Tetsuya, S.; Yoshiki, K.; Masahiro, M.; Masakatsu, N. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−473. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159−1162. (d) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835−4837.

(7) Cobalt-catalyzed arylation of thiazole also furnished products consistent with the "electrophilic regiochemistry": Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607−3610.

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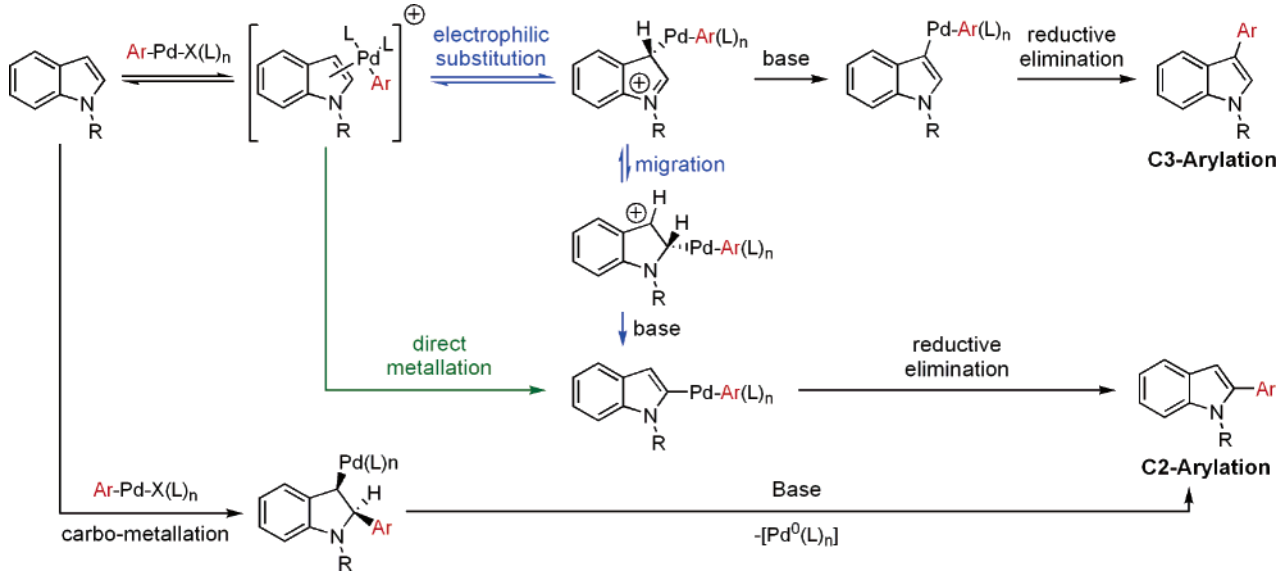
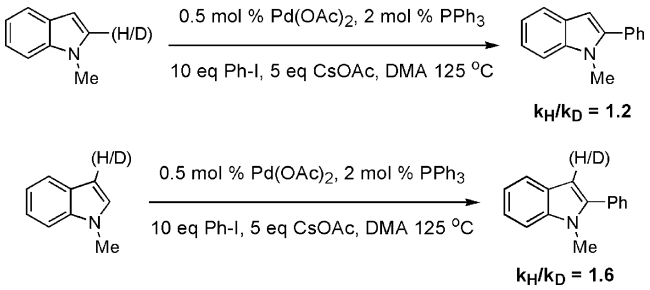
Scheme 3. Possible Reaction Mechanisms in the Arylation of *N*-Alkylindoles



Scheme 4. Kinetic Isotope Effect at the C-2 and C-3 Positions of 1-Methylindole[a]



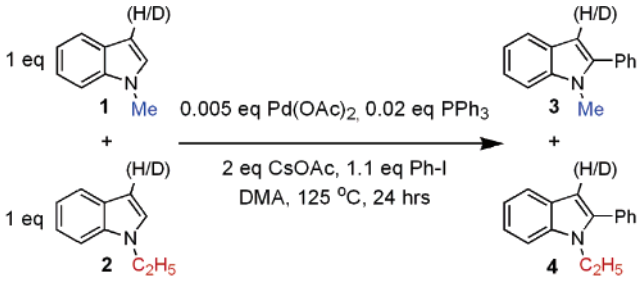
[a] Values determined from three kinetic trials; time points were averaged, and the rate constant was derived from a first-order plot (see Supporting Information).

transformation, the kinetic isotope effect was measured for the 2- and 3-positions of indole.

The Kinetic Isotope Effect at the 2- and 3-Positions of Indole: Kinetic Studies. Both 3- and 2-*deutero*-1-methylindole were synthesized according to literature procedures,[12] and the kinetic constants derived for these substrates were the average of three experiments conducted under pseudo-first-order conditions in substrate (Supporting Information). As usual, these values were compared to those for nondeuterated materials and were used to calculate the kinetic isotope effect (Scheme 4). The KIE for 2-*deutero*-1-methylindole was 1.2, a value too small for the cleavage of this bond to be involved in the rate-limiting step. As a confirmation, the loss of deuterium in the starting material was examined and found significantly slower in comparison to the arylation reaction.

Perhaps more surprising was the KIE of 1.6 obtained for 3-*deutero*-1-methylindole (Scheme 4). Importantly, we confirmed that the deuterium loss in the starting material was significantly slower in comparison to the arylation reaction; 1-methyl-2-phenyl-3-*deutero*-indole was the main product. In addition, no deuterium scrambling was detected via NMR. Interestingly, the larger KIE value was obtained for the 3-position where the substitution does not occur and thereby represents the secondary KIE.

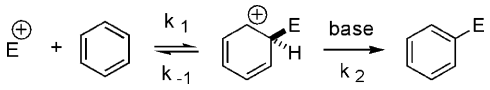
Table 2. Confirmation of the KIE by Competitive Substrate Studies[a]



Exp #	D-labled substrate	3/4 observed	3/4 calculated from KIE
1	none	1.30 +/- 0.004	n/a
2	Me	0.92 +/- 0.02	0.81
3	Et	2.34 +/- 0.03	2.1
4	both	1.43 +/- 0.04	n/a

[a] The product ratios were determined by HPLC versus an internal standard. Values reported are the average of three trials. The KIE value used to calculate the expected product ratios was taken from Scheme 4. Similar results were obtained with 1-methylindole and 1-*n*-octylindole, as well as 1-methylindole and 1-*n*-propylindole (see Supporting Information).

Scheme 5. Generic Electrophilic Substitution Mechanism



The Kinetic Isotope Effect at the 3-Position of Indole: Confirmation by Competitive Reaction Studies. In light of the unexpected results described above, we decided to verify the KIE value at position C-3 by an alternative means, employing the method of competing reactions. According to this technique, two closely related substrate derivatives are submitted to the reaction conditions of interest, in the same flask, and the ratio of products is determined. The $KIE^{(H/D)}$ is then derived from the effect of deuterium labeling, in one of these

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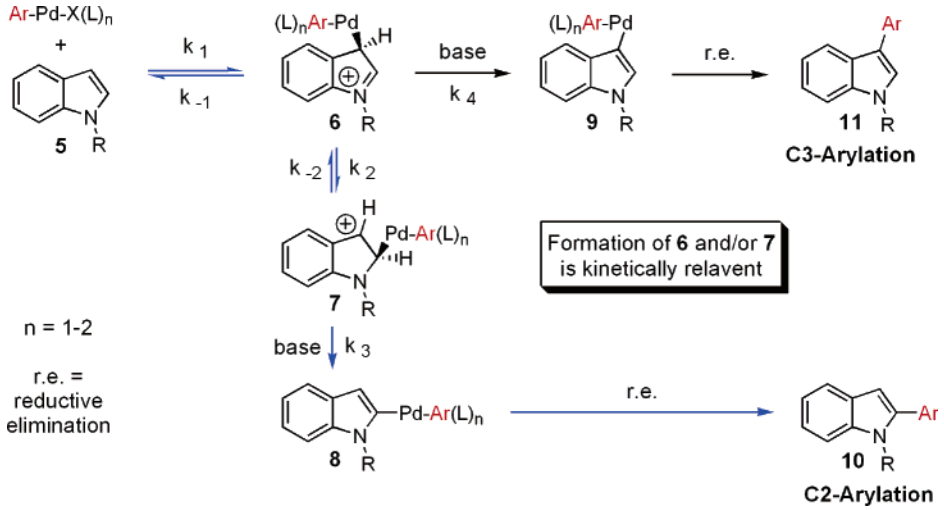
Scheme 6. Electrophilic Pathway for Arylation of Indole



substrates, on the observed ratio of products. The key advantage of this method is that it does not require quantification of rate constants and thus provides an independent confirmation of the KIE. Furthermore, the reactions are conducted under optimized conditions, that is, those used in a typical preparative reaction, as opposed to pseudo-first-order conditions.

In this case, two indole derivatives, 1-methylindole and 1-ethylindole, were chosen, and the inherent reactivity difference between these substrates was determined under the arylation conditions (1.30 ± 0.004 for **3**/**4** ratio, Table 2). Subsequently, two sets of experiments were performed wherein one of the two substrates was replaced with a 3-*deutero*-analogue. For example, in experiment 2 (Table 2), the two substrates were 1-methyl-3-*deutero*-indole and 1-ethylindole. Considering both the intrinsic reactivity difference between 1-methyl- and 1-ethylindole (exp. 1, Table 2) and the KIE determined previously, the calculated product ratio **3**/**4** was 0.81. In simple terms, the higher intrinsic reactivity of 1-methylindole should be overridden by the KIE, and consequently 1-ethylindole should be more reactive. This proved to be the case, and the observed ratio 0.92 ± 0.2 was in a good agreement with the calculated value. A good agreement was also found with the reversed labeling pattern (exp. 3, Table 2). Finally, as a control, the intrinsic reactivity ratio was restored when both substrates were labeled.

Although this method does not measure the KIE as accurately as the kinetic experiments, it does confirm the presence and approximate magnitude of the KIE. The experiments described above substantiate the large secondary KIE at the 3-position of indole (1.6) in the palladium-catalyzed arylation reaction. It is important to reiterate that the competition experiments are conducted under reaction conditions used in a normal preparative reaction, and not the pseudo-first-order ones used in the kinetic measurements.

A Mechanistic Interpretation: Electrophilic Arylation. We are aware that the observed KIE may not be directly related to a single elementary reaction step but instead may reflect a combination of isotope effects stemming from multiple reactions in a complex system.[13,14] Nonetheless, these results do provide some important insights. For instance, they cast serious doubts about the mechanism wherein direct metalation (e.g., via σ-bond metathesis) at position C-2 takes place; this is primarily due to the large KIE at C-3. An alternative mechanism involves the carbopalladation mechanism or the Heck-type mechanism followed by *anti*-dehydropalladation.[15] Carbopalladation of indole, followed by isomerization and *syn*-β-hydride elimination, should also be considered (not shown). A plausible mechanism for the isomerization step is a reversible α-hydride elimination, proceeding via a palladium hydride-carbene intermediate. Although this pathway is known for other transition metals (i.e., Pt, Ru),[16] it has not been observed with palladium; moreover, a large kinetic isotope effect is usually associated with this process (KIE > 4).[17] The most likely candidate, however, seems to be the electrophilic palladation pathway, supported by the kinetic studies and the Hammett plot (see below). The substrate specificity also provides circumstantial evidence for the electrophilic mechanism (e.g., 1-acetylindole was completely inert under the reaction conditions, demonstrating the need for the sufficient electron density in the indole ring, Table 1, entry 6).

The electrophilic pathway may in fact be reconciled with the obtained data if a migration of palladium (C3 → C2) is considered (Schemes 3 and 6). The electrophilic substitution is often considered to be a two-step process consisting of the reversible electrophile−arene complex formation and subsequent deprotonation (Scheme 5). The occurrence and magnitude of the KIE is related to the relative ratio of the individual rate constants (k_1, k_{-1}, and k_2) and varies widely (0−6).[14,18] In most cases, the deprotonation is much faster that the formation of the electrophile−arene complex ($k_2 > k_1$), and, as a consequence, in many electrophilic substitution reactions, like nitration, no KIE is observed.[19] However, if k_{-1} is large as compared to k_2, a steady-state approximation for the concentration of the electrophile−arene complex can be made; that is, its concentra-

(13) (a) Jones, W. D. *Acc. Chem. Res*. **2003**, *36*, 140−146. (b) Lloyd-Jones, G. C.; Slatford, P. A. *J. Am. Chem. Soc*. **2004**, *126*, 2690−2691.
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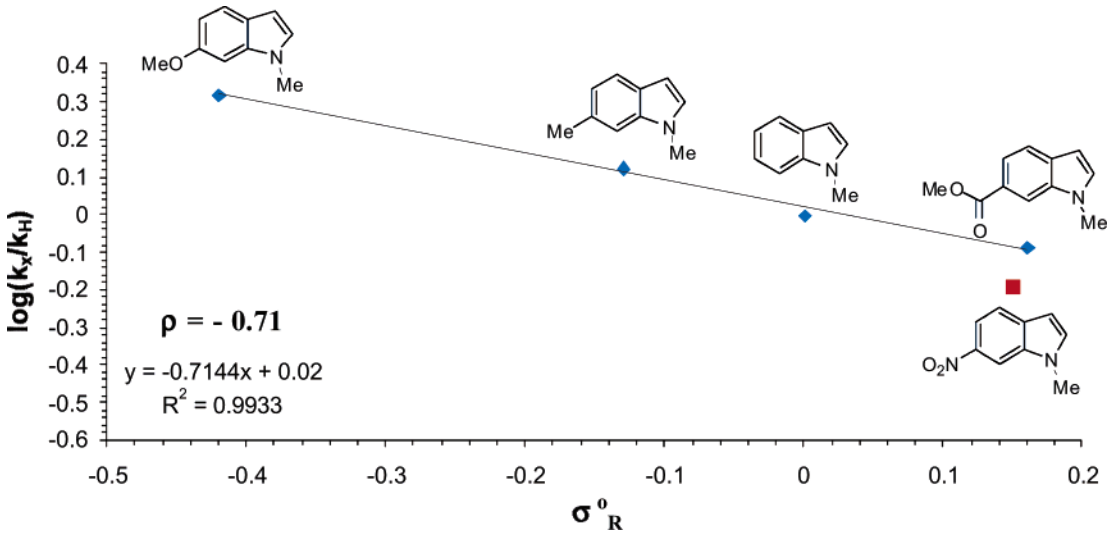
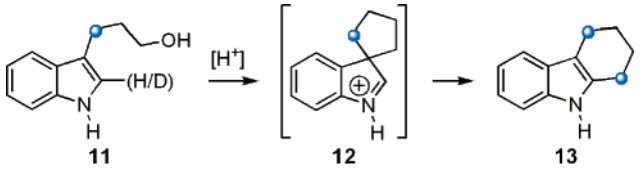


Figure 2. Hammett plot derived for the palladium-catalyzed, selective C-2 arylation of 6-substituted-1-methylindoles. 1-Methyl-6-nitroindole, shown in red, is not included in linear regression.

Scheme 7. Electrophilic Cyclization of 3-(3-Hydroxypropyl)-indole



tion is taken to be very small and constant. The deprotonation then becomes kinetically significant, and as a consequence larger isotope effects are observed, as in the sulfonation of nitrobenzene ($k_H/k_D = 1.59-1.69$).[20] Moreover, very large primary isotope effects have been observed in the mercuration ($k_H/k_D = 6.0$) and palladation ($k_H/k_D = 5.0$) of arenes in acidic media.[21] In these electrophilic metalations, the deprotonation (k_2) is rate-limiting, which is reflected in a large primary KIE. More recently, a large primary KIE has also been measured in the intramolecular palladium-catalyzed cyclization reactions; these latter results are consistent with the electrophilic metalation mechanism.[22]

The electrophilic arylation of indole is, however, more complex than the simple cases mentioned above. Let us consider Scheme 6; for simplicity, the initial oxidative addition of iodobenzene to palladium(0) was omitted as this step does not contribute to the overall rate.

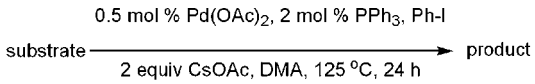
The first step involves the formation of intermediate **6** by the electrophilic addition of an aryl-palladium(II) species to the 3-position of indole. If the reverse step (k_{-1}) is fast as compared to both the forward step (k_1) and the migration (k_2), then the formation of **6** and (or) the migration may become kinetically relevant. In such instance, k_3 must be faster than k_2, and k_4 must be slower than k_2. The unusual features of this system, the large value of the KIE at position C-3 (β-isotope effect) in comparison to that for C-2 (apparent primary KIE), may be explained by this mechanistic interpretation. To the best of our knowledge, 1.6 represents the highest value reported in the literature for a secondary KIE exerted by a single C−D bond (previous values are <1.3, solvolysis reactions).[23] Once again, we stress that the observed value may be a composite of several rate-contributing steps and thus drawing detailed mechanistic conclusions regarding a single elementary step would be erroneous. At the same time, the KIE observed at the 3-position supports the interpretation provided herein, involving the electrophilic attack at C-3, followed by palladium migration.

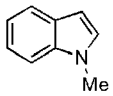
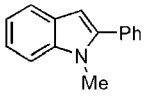
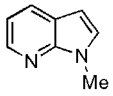
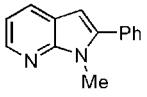
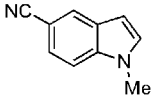
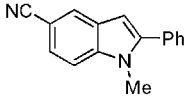
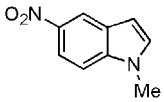
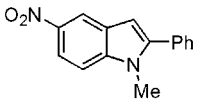
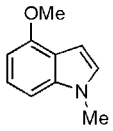
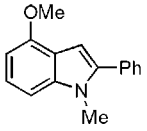
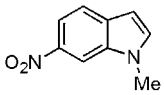
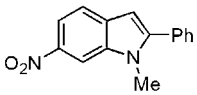
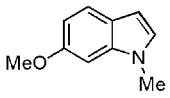
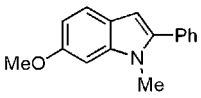
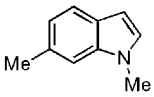
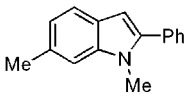
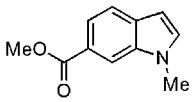
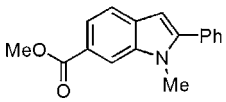
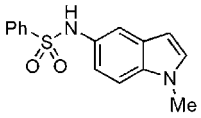
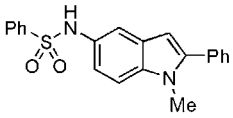
The driving force for this migration is related to stabilization of the carbon−palladium bond by the adjacent nitrogen atom (fast migration of 3-lithio-indole to 2-lithio-indole has also been reported).[24,25] The metal migration around the arene nucleus has long been studied, and the higher stability of organometallic intermediates wherein the metal is attached to an electron-deficient carbon is well recognized.[26] Organopalladium intermediates are known to undergo migrations, as was recently demonstrated by a 1,4-migration in the system derived from *ortho*-iodobiaryls.[27]

Similar 1,2-migration of alkyl groups has been demonstrated in the electrophilic substitution of 3-substituted indoles.[28] For example, formation of intermediate **12** has been supported by

(20) Brand, J. C. D.; Jarvie, A. W. P.; Horning, W. C. *J. Chem. Soc.* **1959**, 3844−3853.
(21) (a) Davidson, J. M.; Triggs, C. *J. Chem. Soc. A* **1968**, 1324−1330. (b) Fung, C. W.; Khorramdel-Vahed, M.; Ranson, R. J.; Roberts, R. M. G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 267−272.
(22) (a) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084−12085. (b) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186−9187.
(23) The large secondary KIE (1.6) has been reported for solvolysis of acetyl chloride. However, this value reflects an accumulative effect of three C−D bonds versus three C−H bonds. (a) Karabatsos, G. J.; Sonnichsen, G. C.; Papaioannou, C. G.; Scheppele, S. E.; Shone, R. L. *J. Am. Chem. Soc.* **1967**, *89*, 463−465. (b) Bentley, T. W. *J. Org. Chem.* **2004**, *69*, 1756−1759.
(24) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757−761.
(25) C-2 selectivity has also been observed in the formation of a zwitterionic intermediate in the reaction of 1-methylindole and $B(C_6F_5)_3$. An analogous C3 → C2 migration was proposed and supported by theoretical calculations, which showed that the C-2 adduct was more stable than the C-3 adduct by 8.4 kcal/mol. Although no experimental evidence has been presented in support of this mechanism, the indole-borane adducts represent relevant models for our system. Focante, F.; Camurati, I.; Nanni, D.; Leardini, R.; Resconi, L. *Organometallics* **2004**, *23*, 5135−5141.
(26) (a) Yudin, L. G.; Pavlyuchenko, A. I.; Kost, A. N. *Zh. Obshch. Khim.* **1969**, *39*, 2784−2784. (b) Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4845−4850.
(27) Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326−14327.
(28) (a) Jackson, A. H.; Smith, P. *J. Chem. Soc., Chem. Commun.* **1967**, 264−266. (b) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439−440.

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



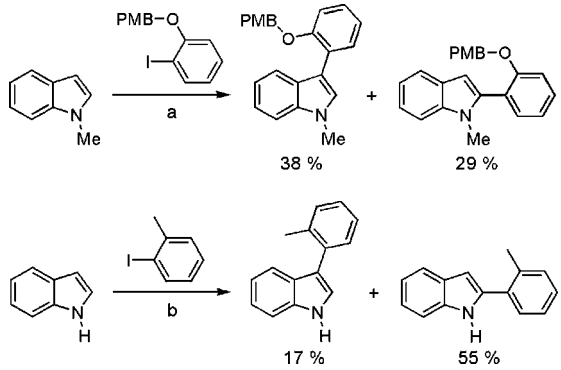
entry	substrate	product	yield
1			88 %
2			85 %
3			78 %
4			61 %
5			51 %
6			56 %
7			81 %
8			82 %
9			69 %
10			24 % (50 %)[a]

[a] All values based on isolated yields; conditions are further described in the Supporting Information. (a) Performed with 0.1 mol % $Pd(OAc)_2$, 0.4 mol % PPh_3; reaction time was 48 h.

labeling experiments, and it has been speculated that the 1,2-migration is rate-limiting in this transformation (Scheme 7).

Hammett Plot of 6-Substituted 1-Methylindoles. The first-order rate dependence on indole concentration allowed for investigating the substitution effect on the reaction rate (Hammett plot) and thus provided strong experimental support for the electrophilic palladation mechanism; that is, the build-up of positive charge at the 3-position gave rise to a negative ρ-value. The reaction rates of a variety of indoles substituted with both electron-releasing and electron-withdrawing groups in the 6-postion, *para* to the reactive center (3-position), were determined. The kinetic data were then used to generate a Hammett plot; as a consequence of the relationship between the 3- and 6-positons of indole, σ°_{R} values were used and found to provide the best correlation with the rate constants (Figure 2). The σ°_{R} values were developed for instances where there is minor perturbation of the substituted benzene-ring system, similar to the instance here.[29] A reasonable relationship between the σ°_{R} values and the rate constants was observed for the substrates tested, with the exclusion of 1-methyl-6-nitroindole. The negative ρ-value derived from the plot is consistent with the electrophilic palladation/migration mechanism.

Scheme 8. Indole Arylation with Sterically Bulky Iodoarenes[a]



[a] Conditions: (a) 0.5 mol % $Pd(OAc)_2$, 2 mol % PPh_3, 1.2 equiv of ArI, 2 equiv of CsOAc, DMA, 150 °C, 24 h. (b) 5 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 2.5 equiv of ArI, 1.2 equiv of MgO, dioxane/DMF (1:2), 150 °C, 18 h.

A similar trend between reactivity and electron density of substituted indoles was also observed in terms of isolated yields obtained in analogous preparative reactions, Table 3. Substrates containing strongly electron-withdrawing substituents exhibited lower yields than their more electron-rich counterparts. For example, the yields in entries 3, 4, and 9 were considerably depressed in contrast to entries 1, 7, and 8 (Table 3). The only notable exemption was entry 5, where significant decomposition of both the starting material and the product was observed. The main consequence associated with the low reactivity of the electron-deficient indoles was the greater production of biphenyl byproducts (this competing pathway is outlined in Scheme 2).

A Mechanistic Rationale for the Observed Regioselectivity. Although the high C-2 selectivity was observed for both 1-alkylindole and an indole magnesium salt (C-2 arylation), haloarene donors substituted in the *ortho*-position afforded a mixture of C-2 and C-3 arylation products (Scheme 8). These results may be rationalized by the electrophilic metalation mechanism in the following terms. In the case of bulky haloarenes, the palladium migration is slower, and as a consequence deprotonation of intermediate **6** (and thus C-3 arylation, Scheme 6) becomes competitive, affording a mixture of regioisomers.

The Development of New C-3 Arylation Protocols. The mechanistic interpretation offered herein serves not only as a rationale for the observed regioselectivity, but also as a guiding hypothesis for the development of new, improved arylation methods. The examples shown in Scheme 8 demonstrate how the selectivity can be altered if the steric bulk of the aryl-palladium(II) intermediate in increased. Consequently, considering intermediate **14** (Figure 3), palladium migration and ultimately the *regio*-course of the arylation may be influenced by several factors. In addition to the steric bulk of the aryl ring

(29) Bromilow, J.; Brownlee, R. T. C.; Lopez, V. O.; Taft, R. W. *J. Org. Chem.* **1979**, *26*, 4766−4770.

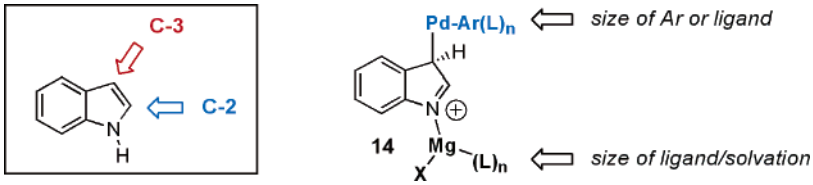
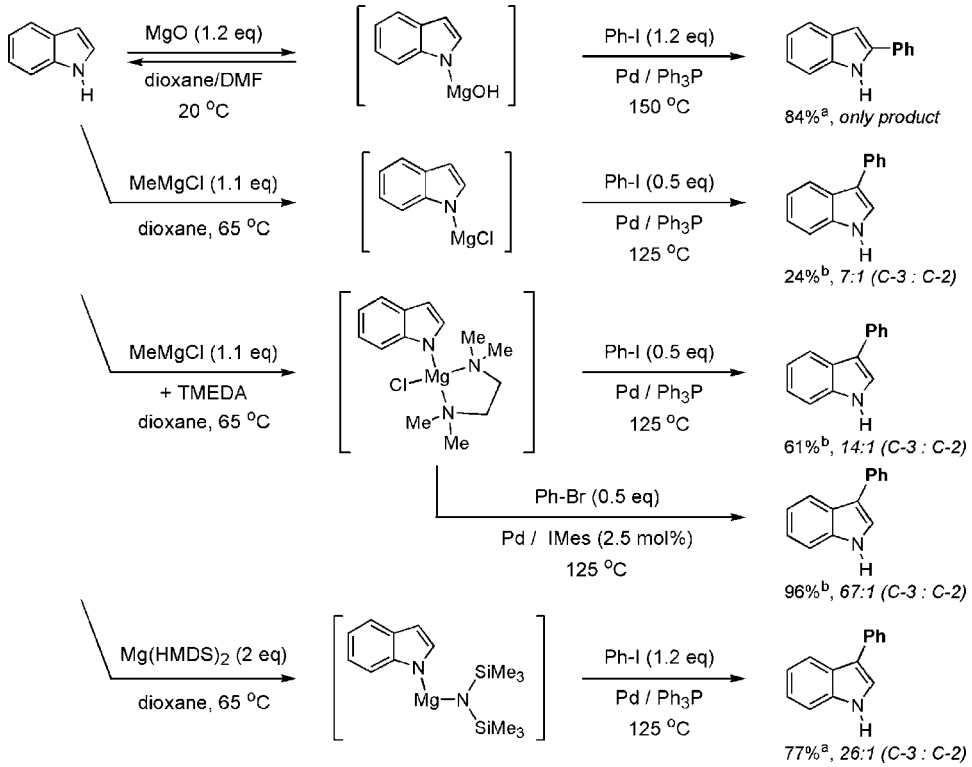


Figure 3. The factors that affect palladium migration and ultimately regioselectivity of indole arylation.

Scheme 9. New Methods for Direct C-3 Arylation of Indole; Regioselectivity Can Be Controlled by the Choice of Magnesium Salt[a]



[a] Conditions: $Pd(OAc)_2$ (2.5 mol %), Ph_3P (10 mol %), IMes (2.5 mol %), 24 h. (a) Reaction yield based on indole. (b) Reaction yield based on PhI. See Supporting Information for detailed procedures. Imes = 1,3-bis-mesitylimidazolyl carbene.

on palladium, as already discussed, these include the ligand on palladium, and the ligand/solvation around the magnesium metal. This hypothesis led us to explore the possibility of direct phenylation of the 3-position, controlled by the choice of the magnesium salt.

As an important hint, we observed that phenylation of the indole Grignard salt prepared from indole and MeMgCl gave a mixture of 3-phenyl- and 2-phenylindole in a 7:1 ratio. This stands in start contrast to the method employing MgO, which afforded 2-phenylindole exclusively (Scheme 9). Clearly, the nature of the magnesium coordination sphere influences the regioselectivity of this reaction. Subsequently, we discovered that the addition of TMEDA (tetramethylethylenediamine) led to formation of 3-phenylindole with high selectivity (14:1), presumably via formation of a sterically demanding magnesium complex (Scheme 9).[30] Although highly selective, the latter methods required a 2-fold excess of the azole magnesium salt as one equivalent serves to neutralize hydrogen halide formed in the arylation reaction. However, this shortcoming was eliminated via formation of a new magnesium salt from indole and $Mg(HMDS)_2$, which led to even higher selectivity (26:1) and allowed indole be used as the limiting agent.

It is important to note that the magnesium indole salts are most likely more complex in structure than depicted in Scheme 9. Although the indole Grignard reagents have been studied for many years, and used primarily in the context of indole C-alkylation reactions,[31] the solution structure of these salts with respect to the magnesium coordination sphere has not been elucidated. These issues will be addressed in the future optimization studies.

Finally, the choice of the palladium ligand also proved important as suggested by our hypothesis. Thus, the use of IMes ligand (1,3-bis-mesitylimidazolyl carbene) in place of Ph_3P led to an improvement in both the yield and the selectivity; furthermore, bromobenzene gave better results in comparison to iodobenzene (Scheme 9).

Thus, a highly selective method for C-3 arylation of indole was developed. A switch from C-2 to C-3 arylation was achieved by the choice of magnesium base. These new condi-

(30) (a) Magnuson, J. A.; Roberts, J. D. *J. Org. Chem.* **1972**, *37*, 133−135. (b) Marsch, M.; Harms, K.; Massa, W.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 696−697. (c) Swiss, K. A.; Liotta, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 9393−9394.

(31) (a) Powers, J. C.; Meyer, W. P.; Parsons, T. G. *J. Am. Chem. Soc.* **1967**, *89*, 5812−5820. (b) Heacock, R. A.; Kasparek, S. *Adv. Heterocycl. Chem.* **1969**, *10*, 43−112. (c) Reinecke, M. G.; Sebastian, J. F.; Johnson, H. W.; Pyun, C. *J. Org. Chem.* **1971**, *36*, 3091−3095. (d) Powers, J. C. *Chem. Heterocycl. Compd.* **1972**, *25*, 127−178.

tions represent an exciting lead for the development of efficient and practical arylation methods.

Conclusions

This paper describes mechanistic investigations aimed at providing a rational explanation for the high C-2 selectivity in the palladium-catalyzed arylation of indoles. It was demonstrated that the reaction was first-order in both the substrate and the catalyst. Moreover, a Hammett plot revealed the negative ρ-value, indicating that a positive charge is accumulated at the 3-position of indole and affording a strong support for the electrophilic palladation mechanism.

The KIE was determined for both C-2 and C-3 positions of indole, yielding the values 1.2 and 1.6, respectively. Interestingly, the larger KIE value was obtained for the 3-position where the substitution does not occur and thereby represents the secondary KIE. These results were confirmed by an independent study, employing the method of competitive reactions. These data support an electrophilic substitution mechanism that features a 1,2-migration of palladium. The electrophilic attack of the arylpalladium species on indole and (or) the migration of palladium represent the slow step(s) of the catalytic cycle. This mechanism has a close parallel in classical electrophilic substitution reactions of indoles substituted in the 3-position. The mechanistic interpretation offered herein served not only as a rationale for the observed regioselectivity, but also as a guiding hypothesis for the development of new arylation methods. It was shown that the choice of magnesium salt affects the regioselectivity of the arylation reaction, presumably via the steric demand of the magnesium coordination sphere. Inspired by these findings, a new catalytic method was designed for selective C-3 arylation of (NH)-indole, complementing the C-2 selective protocol, as well as N-arylation methods. The insight generated in this work will provide the rational basis for the future studies aimed at optimizing the reaction conditions, and expanding the substrate scope and functional group tolerance.

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

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