Regioselective Oxidative Arylation of Indoles Bearing *N*-Alkyl Protecting Groups: Dual C−H Functionalization via a Concerted Metalation−Deprotonation Mechanism

Shathaverdhan Potavathri,[†] Kyle C. Pereira,[†] Serge I. Gorelsky,[‡] Andrew Pike,[†] Alexis P. LeBris,[†] and Brenton DeBoef*,[†]

Department of Chemistry, University of Rhode Island, 51 Lower College Road, Kingston, Rhode Island 02881, and Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie Pvt., Ottawa, Ontario, Canada K1N 6N5

Received August 9, 2010; E-mail: bdeboef@chm.uri.edu

Abstract: The most direct method for synthesizing 2-arylindoles is oxidative coupling of an arene with an indole. We have shown that both the activity and regioselectivity of this cross-coupling reaction are correlated with the acidity of the medium. This insight has been applied to predict the best conditions for the oxidative cross-coupling of *N*-alkylindoles, an important class of substrates that has heretofore been incompatible with the harsh conditions required for oxidative cross-coupling. Both experimental and computational data indicate that the mechanism for C−H palladation of both the indoles and simple arenes is best described as concerted metalation−deprotonation, regardless of the substitution on the arene.

Introduction

Palladium-catalyzed oxidative cross-coupling of arenes is a desirable process because prefunctionalization of either substrate prior to the coupling reaction is not required, thus allowing for a rapid and green synthesis of biaryls.[1−9] A consortium of leading pharmaceutical companies have described such processes as some of the most "aspirational" reactions that remain undeveloped in the "key green chemistry research areas".[10] Arylated indoles represent a privileged class of heterocycles that have diverse applications in pharmaceuticals, fragrances, dyes, and agrochemicals.[11,12] Ideally, the biaryl bond in these compounds could be synthesized by oxidative cross-coupling, but such reactions, involving double C−H bond functionalization, are difficult because the oxidative conditions often decompose electron-rich *N*-alkylindole substrates. Herein, we disclose that tuning the acidity of the reaction medium enables the synthesis of arylated indoles via oxidative cross-coupling and prevents the
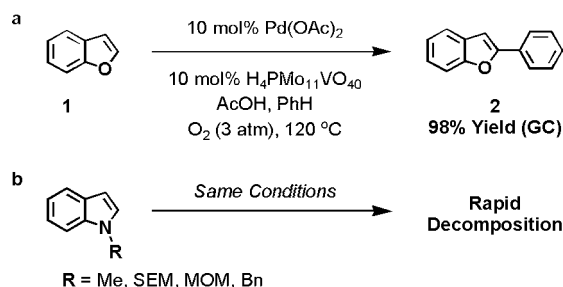

Figure 1. Limits of current oxidative coupling technology. SEM = 2-(trimethylsilyl)ethoxymethyl; MOM = methoxymethyl; Bn = benzyl.

oxidative decomposition of the important but sensitive indole substrates and products.

We have previously shown that benzofuran (**1**) can be oxidatively cross-coupled with benzene (used as a cosolvent) to regioselectively form 2-phenylbenzofuran (**2**) (Figure 1, reaction **a**).[13] The reaction is notable because of its high yield, short reaction time, and use of molecular oxygen as the terminal oxidant. However, our initial efforts to apply these optimized conditions to indoles were unfruitful. The acidic, oxidizing conditions that were ideal for benzofurans rapidly decomposed *N*-alkylindole substrates (reaction **b**).[14]

Subsequently, both we and the Fagnou group achieved intra- and intermolecular oxidative arylation of *N*-acetylindoles by replacing the acidic medium with a neutral cosolvent[15] or buffering it with either AgOAc or Cu(OAc)$_2$, which can act as

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[†] University of Rhode Island.
[‡] University of Ottawa.

(1) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.
(2) Chen, X.; Engle, K.; Wang, D.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
(3) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673.
(4) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
(5) Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, 949.
(6) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.
(7) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376.
(8) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.
(9) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837.
(10) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
(11) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.
(12) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.

(13) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.
(14) Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, *73*, 2641.
(15) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050.
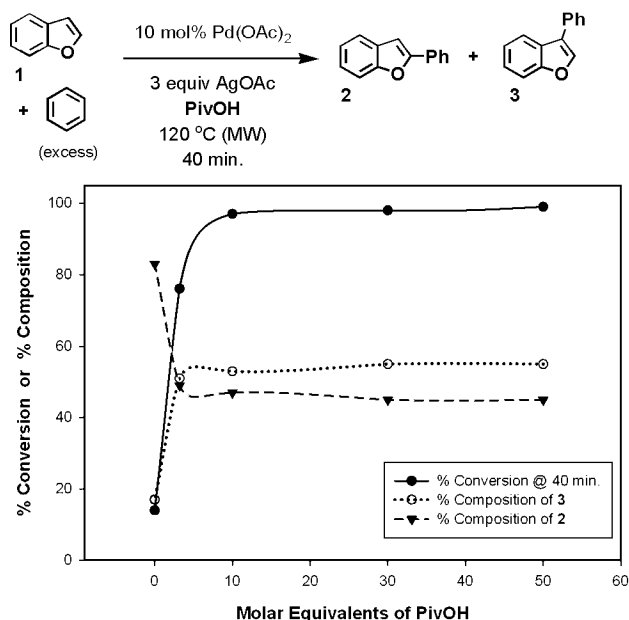
Figure 2. Oxidative coupling of benzofuran (**1**) and benzene as a function of acid concentration.

both an oxidant and a weak base.[15−17] Additionally, both groups found that the selectivity for arylation at either the 2- or 3-position of the indole was influenced by the choice of oxidant, with AgOAc favoring the 2-aryl product and Cu(OAc)$_2$ favoring arylation at the 3-position.[15,16] However, none of these conditions were compatible with *N*-alkylindoles, as they provided negligible yields and a loss of regiochemical control, regardless of the oxidant.

In light of this precedent, we hypothesized that the reactivity of the oxidative cross-coupling could be modulated as a function of the medium's acidity. This was verified by studying the oxidative coupling of **1** with benzene as the concentration of organic acid in the reaction mixture was modulated (Figure 2). **1** was an ideal substrate for these studies because of its reactivity under all of the conditions and because it was not prone to oxidative decomposition. PivOH was used as the acidic additive because it minimized the formation of acetoxylated byproduct.[18]

The most active conditions for the oxidative arylation of **1** were the most acidic. As the concentration of organic acid was lowered relative to the concentration of AgOAc, which served as both a stoichiometric oxidant and a weak base, the rate of the reaction was retarded. All of the reactions containing PivOH and AgOAc produced nearly a 1:1 mixture of the two regiomeric products (**2** and **3**), but when PivOH was removed from the reaction, the 2-aryl product was preferentially formed (**2**/**3** = 4:1). Consequently, we concluded that both the activity and regioselectivity of the oxidative cross-coupling are correlated with the acidity of the reaction medium.

Results and Discussion

Reaction Discovery. In light of these trends, we hypothesized that sensitive indole substrates might be amenable to oxidative cross-coupling with arene solvents using the "buffered" condi-

(16) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.
(17) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.
(18) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.

Table 1. Discovery and Optimization of Regioselective Oxidative Arylation with Electron-Rich Indoles
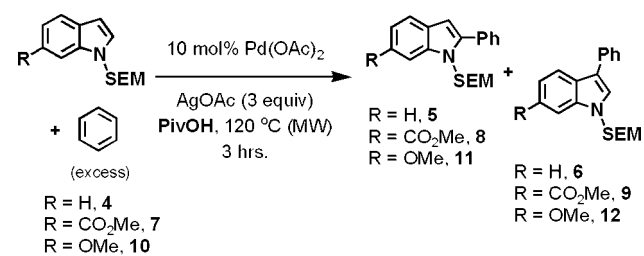
entry	R	equiv of PivOH	conv. (%)[a]	yield (%)[a]	ratio[b]
1	H	0	62	43	2.1:1
2	H	1	81	58	2.2:1
3	H	2.5	96	69	2.6:1
4	H	5	98	65	2.5:1
5	CO$_2$Me	2.5	100	97	8.7:1
6	OMe	2.5	100	56	2.7:1

[a] Unreacted starting material and products were isolated by flash chromatography. [b] **5**/**6** (entries 1−4), **8**/**9** (entry 5), or **11**/**12** (entry 6), as determined by GC.

tions containing nearly equal amounts of PivOH and AgOAc, but we were cognizant of the regioselectivity issues that could be observed. Gratifyingly, when the "buffered" conditions were applied to the oxidative cross-coupling of *N*-SEM-indole **4**, the reaction proceeded with modest yield and regioselectivity (Table 1, entries 2−4). Reactions containing no PivOH failed to completely convert the starting material (entry 1). The optimal conditions contained a slight excess of AgOAc relative to PivOH, which likely prevented the acid-promoted oxidative decomposition of the indole substrate and products.

The regioselectivities of the indole reactions were not dramatically affected by the acidity of the reaction medium; rather, they were modulated by substitution on the indole substrate. The electron-withdrawing ester functionality (**7**) tripled the regioselectivity of the oxidative arylation, favoring the 2-phenylindole product (**8**), and significantly increased the overall yield (entry 5). Substitution with an electron-donating methyl ether (**10**) had a minimal effect on the regioselectivity and a slight deleterious effect on the yield (entry 6).

Scope of the Oxidative Cross-Coupling Reaction. The optimized oxidative coupling conditions were amenable to *N*-alkylindoles decorated with a wide variety of functional groups (Table 2). Indoles substituted with an N-protecting group such as SEM, benzyl, or MOM were all amenable to the oxidative coupling reaction (**5**, **13**, **14**). Protection of the indole with the electron-withdrawing tosyl group did not prevent the oxidative coupling (**16**). *N*-Methylindole provided a diminished yield despite rapid conversion, which implies that oxidative decomposition of the starting material, the product, or both may be a competitive process for this substrate.

Indoles bearing electron-withdrawing groups (**8**, **18−21**) provided higher yields and regioselectivities than those containing electron-donating groups (**10**, **23**, **24**). Notably, *N*-SEM-7-azaindole, which could potentially deactivate the catalyst via ligation, underwent the coupling with good regioselectivity and yield (**22**).

A variety of functional groups on the benzene substrate were also tolerated. Ortho-, meta-, and para-disubstituted benzenes provided only one regiomeric product (**25−28**). However, the steric interaction associated with the coupling of *p*-xylene diminished its yield (**28**). Additionally, there appears to be a limit to the electron density of the arene that can be coupled to

Table 2. Scope of the Oxidative Arylation Reaction[a]

Variation of *N*-Substituent[b]

5 SEM
69% yield
(3:1)

13 Bn
57% yield
(4:1)

14[c] MOM
56% yield
(4:1)

15 Me
31% yield
(4:1)

16 Ts
49% yield
only isomer

Variation of Indole Substrate[b]

MeO₂C — **8** SEM
97% yield
(9:1)

O₂N — **18** SEM
88% yield
only isomer

O₂N — **19** SEM
77% yield
(28:1)

NC — **20** SEM
73% yield
(13:1)

OHC — **21** SEM
67% yield
(4:1)

22 SEM
72% yield
(8:1)

MeO — **11** SEM
56% yield
(3:1)

MeO — **23** SEM
48% yield
(4:1)

Me — **24** SEM
61% yield
(3:1)

Variation of Benzene Substrate[b]

NC — **25** SEM, Me Me
76% Yield
only isomer

O₂N — **26** SEM, Me Me
73% yield
only isomer

O₂N — **27** SEM, Me Me
65% yield
only isomer

O₂N — **28** SEM, Me Me
23% yield
only isomer

O₂N — **29** SEM, OMe OMe
14% yield
only isomer

O₂N — **30** SEM, Cl Cl
65% yield
only isomer

O₂N — **31** SEM, F F F F
44% yield
(2:1)

[a] Conditions: 0.15 mmol of indole, 4 mL of arene, 10 mol % Pd(OAc)₂, 3 equiv of AgOAc, 2.5 equiv of PivOH, 120 °C (microwave). [b] Only the major isomer is shown. The minor isomer is the 3-arylindole. Yields and regioselectivities were obtained by isolation of both isomers following flash chromatography. [c] *N*-MOM-indoles behaved similarly to *N*-SEM indoles in that the 5-NO₂ derivative of **14** was phenylated exclusively at the 2-position with a better yield (**17**, 68%; see the Supporting Information for details).

the indole, as the yield for coupling of *o*-xylene (**26**) was 5 times greater than that of veratrole (**29**). Interestingly, benzene
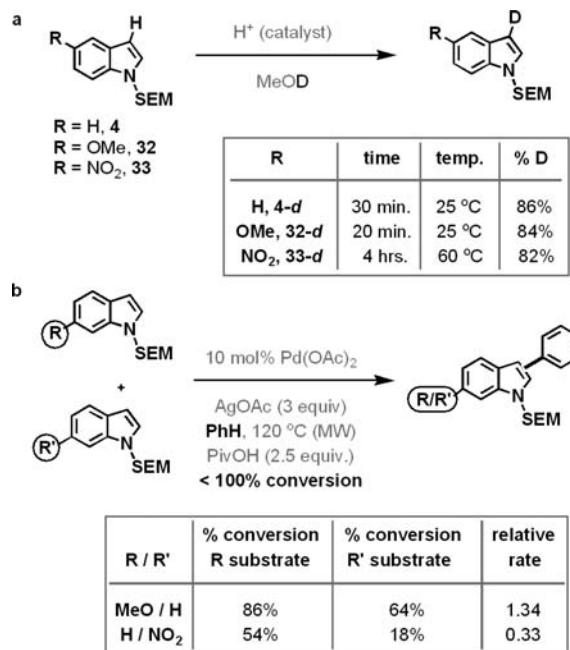
R	time	temp.	% D
H, 4-*d*	30 min.	25 °C	86%
OMe, 32-*d*	20 min.	25 °C	84%
NO₂, 33-*d*	4 hrs.	60 °C	82%

R / R'	% conversion R substrate	% conversion R' substrate	relative rate
MeO / H	86%	64%	1.34
H / NO₂	54%	18%	0.33

Figure 3. Probing the mechanism of indole palladation: (a) deuteration study; (b) competition experiment. In (b), the reaction time was ∼15 min, and the conversion was computed from GC data. The competing reactions displayed pseudo-zeroth-order kinetics, so the relative rates could be calculated directly from the conversions (the data were normalized to the rate for unsubstituted indole).

substrates bearing halogens, which are generally considered to be deactivated for electrophilic aromatic substitutions, could also be oxidatively cross-coupled with indoles, albeit in slightly diminished yields (**30**, **31**).

Mechanism of Indole Palladation. In general, two C−H bond activation mechanisms are commonly used to describe the substitution of arenes by electrophilic metals such as Pd(II). The first involves electrophilic palladation via an SₑAr process. For indoles, this proposed mechanism involves the initial palladation at the nucleophilic 3-position, after which a 1,2-migration of the metal to the 2-position of the substrate can follow.[19] Alternatively, palladation via a concerted metalation−deprotonation (CMD) process with a six-membered transition state has been described as a possible mechanism in the metalation of many heterocyclic arenes, and the regioselectivity of such a process for *N*-methylindole substrates has been reported recently.[20]

To probe these two mechanistic possibilities, we conducted a series of experiments (Figure 3). We first used a simple deuteration study (reaction **a**) to confirm that *N*-SEM-indoles containing both electron-donating and electron-withdrawing groups are nucleophilic at the 3-position. This showed that regardless of the substitution on the indole's benzenoid ring, palladation of the indole substrate does not occur via direct electrophilic substitution at the 2-position (i.e., by a pyrrole-like mechanism). However, the longer reaction times required for deuterium incorporation into **33** confirmed the well-known fact that the electrophilic aromatic substitution of electron-poor indoles at the 3-position (e.g., **33**-*d*) is less favorable than that of electron-rich substrates (e.g., **32**-*d*).

(19) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

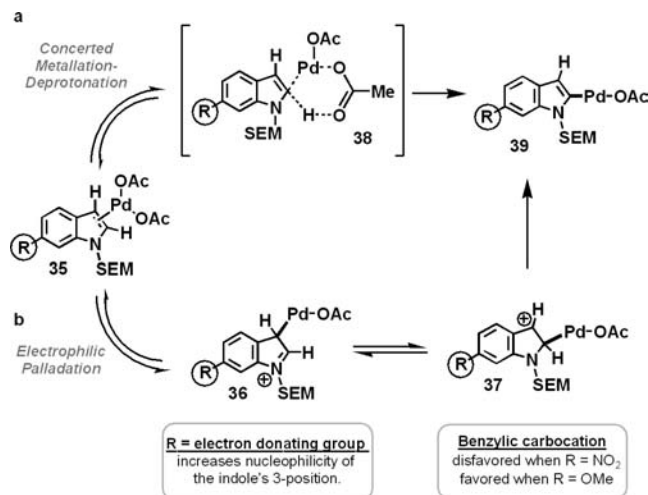(20) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

Figure 4. Potential mechanisms for palladation of indole.

Table 3. Distortion/Interaction Analysis (kcal mol^{-1}) for the Lowest-Free-Energy CMD Transition States at the C2 sites of *N*-Methylindoles Bearing an Electron-Donating or -Withdrawing Group at the 6-Position

entry	R	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$	E_{dist}(ArH)	E_{dist}(Pd)^a	$-E_{int}$	$B_{Pd-C2}{}^b$
1	OMe	15.7	5.5	39.1	25.7	59.2	0.813
2	H	17.7	7.6	36.1	24.8	53.3	0.794
3	NO$_2$	20.2	10.1	31.4	23.7	45.0	0.742

^{a} Pd(OAc)$_2$. ^{b} Mayer bond order for the Pd−C$_{Ar}$ interaction in the transition state.

A competition experiment between *N*-SEM-6-methoxyindole (**10**) and *N*-SEM-indole (**4**) (Figure 3, reaction **b**) found that the indole bearing an electron-donating group (**10** → **11**) reacted 1.34 times faster than its unsubstituted counterpart. Additionally, *N*-SEM-6-nitroindole (**34**) reacted 3 times slower than its unsubstituted counterpart. These data seem to indicate that during the course of the oxidative coupling reaction, palladation of the indole substrate proceeds via an electrophilic substitution process. As described previously, the electrophilic palladium should attack at the aromatic heterocycle's nucleophilic 3-position, after which a 1,2-migration of the metal to the indole's 2-position can occur (Figure 4, mechanism **b**). However, such a mechanism is not in line with the observations shown in Table 2, where the attachment of electron-withdrawing groups to the indole's 6-position, which should destabilize the product of such a migration (**37**), actually enhanced the formation of the 2-arylated indole products (compare **11** with **18** in Table 2). Consequently, we hypothesized that indole substrates bearing both electron-donating and electron-withdrawing groups are palladated by the aforementioned CMD mechanism (Figure 4, mechanism **a**).

Computational analysis of the palladation of substituted *N*-methylindoles corroborated the CMD mechanism. The reaction barriers (Gibbs free energies of activation, $\Delta G^{\ddagger}$) were evaluated using indoles bearing electron-donating and electron-withdrawing groups (Table 3). In accord with the experimental outcomes, the $\Delta G^{\ddagger}$ value for the CMD pathway was found to be 2.0 kcal mol^{-1} lower for the indole bearing the 6-methoxy group (entry 1) and 2.5 kcal mol^{-1} higher for the indole bearing the 6-nitro group (entry 3) relative to the nonsubstituted indole (entry 2).

To explain the impact of electron-donating and -withdrawing groups on the direct arylation reactivity of indoles, the contribu-
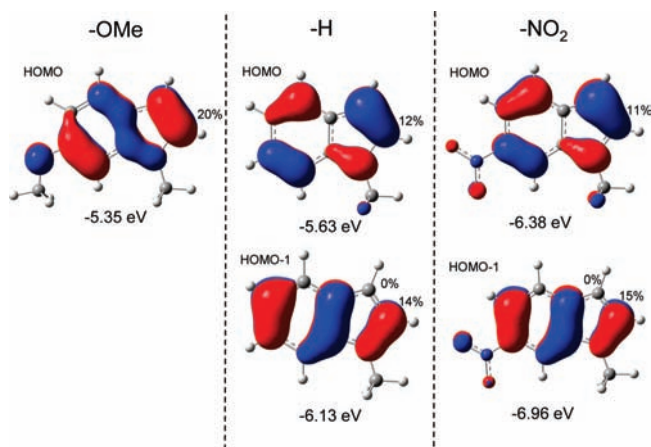

Figure 5. Occupied frontier orbitals for the indoles that contribute to the interaction with the Pd(II) catalyst in the CMD transition state. The C2 atomic contribution (%) and the energy (eV) for each orbital are shown.

tions to $\Delta G^{\ddagger}$ were calculated using a distortion/interaction analysis of the corresponding transition states. In this approach, the distortion energies E_{dist} associated with distortions of the arene (ArH) and the catalyst [Pd(OAc)$_2$] from their ground-state geometries to the geometries in the transition state as well as the electronic interaction energy E_{int} between Pd(OAc)$_2$ and ArH in the CMD transition state were evaluated (Table 3). The OMe group on the indole increased E_{dist}(ArH) by 3.0 kcal mol^{-1} (entry 1 vs 2). On the other hand, the NO$_2$ group on the indole decreased E_{dist}(ArH) by 4.7 kcal mol^{-1} (entry 3 vs 2). The value of E_{dist}(Pd) (between 23.7 and 25.7 kcal mol^{-1}) showed little variation for reactions of different indoles. The presence of an electron-donating or -withdrawing substituent was also found to influence the interaction energy E_{int} (Table 3). E_{int} became more negative for the indole bearing an OMe substituent and less negative for the indole bearing a NO$_2$ substituent. The analysis of the covalent interactions in the CMD transition states also indicated that the Pd−C bond order decreases in order OMe > H > NO$_2$. Since the influence of the substituents on E_{dist}(ArH) is weaker than their influence on E_{int}, the observed reactivity trend (OMe > H > NO$_2$) for these indole substrates is caused by the change in E_{int} between the indole and the Pd(II) catalyst. The changes in E_{int} can be traced to how these electron-donating and -withdrawing groups tune the energy and electron distribution of the two highest occupied molecular orbitals of the indole (the HOMO and HOMO-1) upon substitution (Figure 5).

According to the analysis of fragment orbital interactions in the CMD transition state, significant contributions to indole-to-metal charge transfer interactions involve only two donor orbitals (the HOMO and HOMO-1) of the indole. When the CMD transition state is formed, the electron populations of these two orbitals change by 13.0 and 10.0%, respectively. The OMe substituent increases the energy of the HOMO to −5.35 eV and increases the HOMO density at the C2 site (20%). As a result, for OMe-indole, the HOMO becomes the only donor orbital that participates in indole-to-metal charge transfer, and upon the formation of the CMD transition state, the population of this orbital changes by 21.1%. On the other hand, the NO$_2$ substituent lowers the energies of the occupied orbitals of indole. As a result, the electronic interaction between NO$_2$-indole and Pd(II) is weakened, and E_{int} is only −45.0 kcal mol^{-1} (Table 3, entry 3), which can be compared with the E_{int} value of −59.2 kcal mol^{-1} in OMe-indole.

Mechanism of Palladation of the Simple Arene Substrate. The ability to couple both electron-rich and electron-poor arenes to indole substrates is incongruent with our previous work (Table 2, **25−31**), in which acidic conditions could not couple heteroaromatic substrates with pentafluorobenzene[13] and basic conditions could not couple *N*-acetylindoles with anisole.[15] To explain these phenomena, we hypothesized that the optimized, buffered reaction conditions allowed for mechanistic promiscuity whereby the simple arene, like the indole substrate, could be palladated by either an electrophilic substitution or proton abstraction process. Alternatively, the palladation of the simple arene could proceed via a CMD mechanism.[20]

To test these two hypothetical reaction pathways, we performed a competition experiment in which indole **34** was mixed with equimolar amounts of *o*-dichlorobenzene (**40**) and *o*-xylene (**41**) (Figure 6, reaction **a**). Our optimal conditions for oxidative cross-coupling resulted in a nearly equal mixture of products (**26**/**30** = 1.1:1). This product ratio did not change significantly as the acidity of the medium was modulated.

This unpredicted lack of chemoselectivity was further exemplified by the regioselective competition reaction that occurs in the oxidative coupling of *o*-trifluoromethyltoluene (**42**) (Figure 6, reaction **b**). Interestingly, a 1.4:1 ratio of products **43** and **44** was observed, with the major product arising from palladation para to the methyl group. The results of these competition studies, in which there was no marked chemoselectivity, are not consistent with either an electrophilic palladation mechanism or a proton abstraction mechanism involving the buildup of charged intermediates.

Computational analysis of arene **42** provided insight into the mechanism by which it is palladated (see the Supporting Information for details). The carbon atom para to the methyl group contains the largest partial negative charge, so it should be most amenable to palladation via an S_EAr mechanism. The anion formed by abstraction at the position para to the trifluoromethyl group is more stable than that formed by abstraction para to the methyl group, indicating that the former proton would be more easily abstracted by a traditional acid−base reaction. Interestingly, the lengths of these two C−H bonds were computed to be identical (1.075 Å). Previous computational and experimental work has shown the CMD mechanism is favored by longer C−H bonds.[20] Thus, the CMD mechanism predicts the minimal selectivity that was observed in the oxidative coupling of **42**. Importantly, these computations can be performed using readily available, user-friendly software (such as *Spartan*[21]) and a desktop/laptop computer, indicating that predictions about the reactivity of a given substrate in palladation reactions involving CMD mechanisms can easily be obtained by a conventional synthetic organic chemist.

Finally, to differentiate between the possibility of two competing mechanisms and the action of a single, unique mechanism, we performed kinetic isotope effect (KIE) studies of the oxidative coupling reaction and varied the concentration of the PivOH (Figure 6, reaction **c**). It has been previously suggested that electrophilic palladation processes in which minimal C−H bond breaking is involved in the transition state (KIE < 3) should be favored by higher concentrations of acid (usually AcOH but in our case PivOH). Conversely, reactions containing less acid should be more basic and should favor a
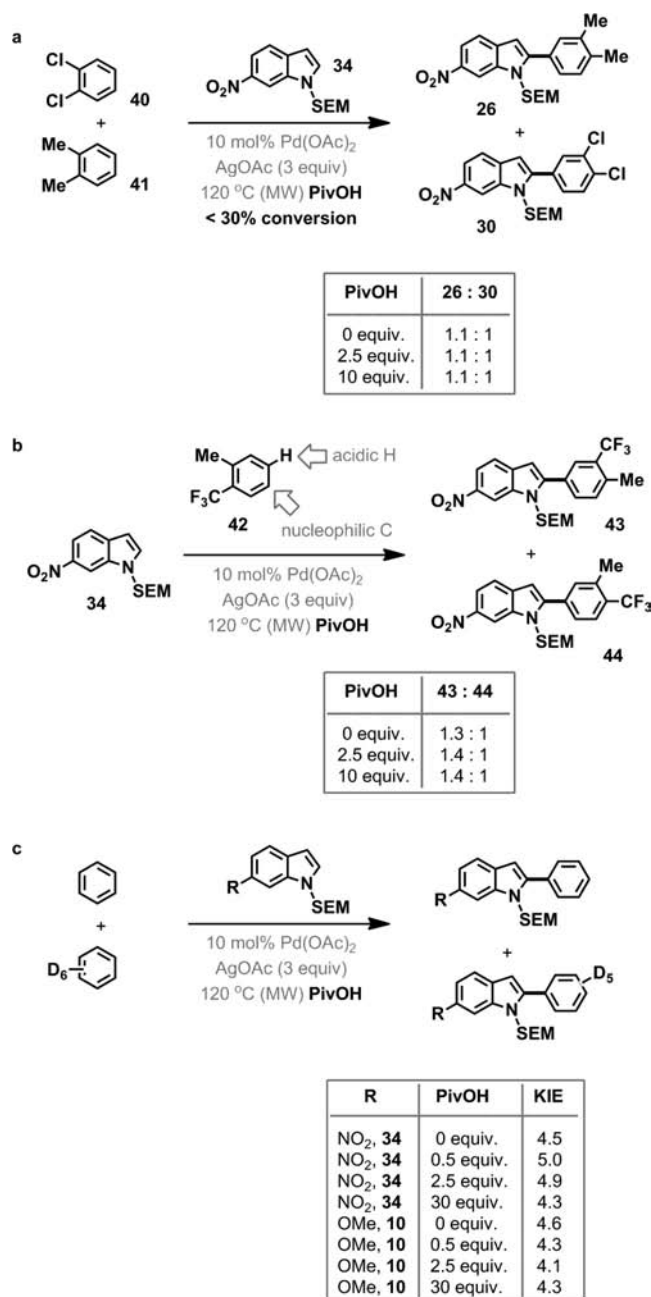
(21) *Spartan '08*; Wavefunction, Inc.: Irvine, CA, 2008.

Figure 6. Probing the mechanism of palladation of the simple arene substrate.

proton abstraction process, where considerable C−H bond breaking can be observed in the transition state (KIE > 3).[22,23] As predicted, large KIE values were observed in a competition reaction using equimolar amounts of benzene and benzene-d_6, indicating that cleavage of the solvent arene's C−H bond is rate-determining. Furthermore, the data show that the KIE for the oxidative coupling did not vary dramatically as a function of the acidity of the medium, which indicates that the palladation of the simple arene occurs via a single CMD mechanism as

(22) Campeau, L.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.
(23) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727.

opposed to competing electrophilic palladation and proton abstraction mechanisms.

Conclusions

This work is one of a small number of studies involving complementary experimental and computational evidence supporting a C−H palladation mechanism involving a concerted metalation−deprotonation (CMD) mechanism.[20] Other researchers have described similar metalation processes, which have been called proton abstraction[24−26] or σ-bond metathesis,[27] and numerous palladium-catalyzed C−H functionalization reactions have been characterized as having both the ability to react with both electron-rich and electron-poor heterocycles and KIEs in the 3−5 range. Consequently, we hypothesize that the CMD mechanism demonstrated herein may not be limited to a select set of reactions but rather may operate in a variety of C−H functionalizations. Our work further validates the idea that the CMD mechanism, though often called proton abstraction, is not traditional acid−base chemistry, as it is not affected by the acidity of the reaction medium. Rather, a given C−H bond's propensity to participate in a CMD process is better predicted by the length of the bond as opposed to its relative acidity.

In summary, we have discovered a mild and efficient method for oxidative cross-coupling of indoles with benzene substrates via double C−H functionalization. Both the indole and simple arene substrates are palladated by CMD processes. This work represents the first example of the operation of a CMD mechanism in an acidic reaction medium, as is common for oxidative cross-coupling reactions. However, we have shown that the acidity of the medium does not significantly affect the CMD process for the palladation of simple, benzene-derived arenes but does affect the regioselectivity of the palladation of

indole-derived arenes in oxidative cross-coupling reactions. Future work in our laboratory will seek to develop oxidative cross-coupling reactions for new classes of high-value substrates and will be guided by the mechanistic investigations that have been disclosed in this article.

Methods

Representative Procedure. A magnetically stirred solution of 1-[2-(trimethylsilyl)ethoxymethyl]indole-6-carboxylate (64 mg, 0.21 mmol), palladium acetate (4.7 mg, 0.021 mmol), silver acetate (104 mg, 0.63 mmol), and 2,2-dimethylpropanoic acid (53 mg, 0.52 mmol) in 5 mL of benzene was microwave-heated at 120 °C for 3 h. After evaporation of the solvent, the mixture was then diluted with 40 mL of water and extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were washed with two 40 mL portions of brine followed by two portions of 40 mL of water and then dried with anhydrous magnesium sulfate. After filtration, the solvent was removed at reduced pressure, and the crude product was purified by column chromatography to give pure **8** (70 mg, 87% yield) and the corresponding 3-phenyl product (8 mg, 10% yield). Both compounds were analytically pure, as determined by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (see the Supporting Information for complete characterization).

Supporting Information Available: Complete experimental and computational details, compound characterization data, and analysis of product purity. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.
(25) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.
(26) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.
(27) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651.