THE UNIVERSITY OF RHODE ISLAND

University of Rhode Island
DigitalCommons@URI

Chemistry Faculty Publications

Chemistry

2010

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

Shathaverdhan Potavathri
University of Rhode Island

Kyle C. Pereira
University of Rhode Island

See next page for additional authors

Follow this and additional works at: https://digitalcommons.uri.edu/chm_facpubs

This is a pre-publication author manuscript of the final, published article.

Authors

Shathaverdhan Potavathri, Kyle C. Pereira, Serge Gorelsky, Andrew Pike, Alexis P. LeBris, and Brenton DeBoef

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 Gorelsky[‡], Andrew Pike[†], Alexis P. LeBris[†], and Brenton DeBoef[*,†]

Department of Chemistry University of Rhode Island 51 Lower College Road Kingston, RI USA, 02881

Centre for Catalysis Research and Innovation Department of Chemistry University of Ottawa, 10 Marie Curie Pvt. Ottawa, Ontario Canada, K1N 6N5 Phone: (+01) 613-562-5800 ext. 6353 Fax: (+01) 613-562-5170 sgorelsk@uottawa.ca

Abstract

The most direct method for synthesizing 2-arylindoles is the oxidative coupling of an arene with an indole. We have shown that both the activity and regioselectivity of these cross-coupling reactions are correlated to 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 was heretofore 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 (CMD), regardless of the substitution on the arenes.

Introduction

The palladium catalyzed oxidative cross-coupling of arenes is a desirable process because the prefunctionalization of either substrate is not required prior to the coupling reaction; 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 allows for the synthesis of arylated indoles via oxidative cross-coupling and prevents the oxidative decomposition of the important, but sensitive, indole substrates and products, and that these reaction conditions allow for three distinct palladation mechanisms.

[*]Phone: (+01) 401-874-9480 Fax: (+01) 401-874-5072 bdeboef@chm.uri.edu.
[†]University of Rhode Island
[‡]University of Ottawa

We have previously shown that benzofuran (**1**) can be oxidatively cross-coupled with benzene (used as a co-solvent) to regioselectively form 2-phenylbenzofuran (**2**) (Figure 1, reaction **a**).13 The reaction was 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 the intra- and intermolecular oxidative arylation of *N*-acetylindoles by replacing the acidic media with a neutral co-solvent15 or by buffering it with either AgOAc or Cu(OAc)$_2$, which can act as both oxidants and weak bases.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: 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, providing 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 benzofuran (**1**) with benzene as the concentration of organic acid in the reaction was modulated (Figure 2). **1** was an ideal substrate for these studies because of its reactivity in 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 by-products.18

The most active conditions for the oxidative arylation of **1** were the most acidic. As the concentration of organic acid was lowered with respect to the concentration of AgOAc, which served as both a stoichiometric oxidant and a weak base, the rate of the reaction was retarded. All 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 3-aryl product was preferentially formed (4:1, **3**:**2**). Consequently, we concluded that both the activity and the regioselectivity of the oxidative cross-coupling were correlated to 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" conditions which contained near 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 compared 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 (**8**) and significantly increased the overall yield (entry 5). Substitution with an electron-donating methyl ether (**10**) had 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 *N*-protecting groups such as benzyl, MOM and SEM 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, coupled with good regioselectivity and yield (**22**).

A variety of functional groups were also tolerated on the benzene substrate. *Ortho*, *meta* and *para*-disubstituted benzenes provided only one regiomeric product (**25**–**28**). However, the steric interaction associated with the coupling of *para*-xylene diminished its yield (**28**). Additionally, there appears to be a limit to the electron density of the arene that can be coupled to the indole, as the yield for coupling *ortho*-xylene (**26**) was five times greater than that of veratrole (**29**). Interestingly, benzene 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 the electrophilic palladation via a S_EAr process. For indoles, this proposed mechanism involves the initial palladation at their nucleophilic 3-position, after which a 1,2-migration of the metal to the substrate's 2-position can follow.[19] Alternatively, palladation via a concerted metalation-deprotonation (CMD) process with a 6-member 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 confirmed that *N*-SEM-indoles, which contain both electron-donating and electron-withdrawing groups, are nucleophilic at their 3-position using a simple deuteration study (reaction **a**). This showed that, regardless of the substitution on the indole's benzenoid ring, the palladation of the indole substrate does not occur via direct electrophilic substitution at the 2-position, 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 their 3-position (*e.g.* **33-*d***) was less favourable than that of electron-rich substrates (*e.g.* **32-*d***).

A competition experiment between *N*-SEM-6-methoxyindole (**10**) and *N*-SEM-indole (**4**) found that the indole bearing an electron donating group (**10** → **11**) reacted 1.34 times faster than its unsubstituted counterpart (Figure 3, reaction **b**). Additionally, *N*-SEM-6-nitroindole (**34**) reacted three times slower than its unsubstituted counterpart. These data seem to indicate that, during the course of the oxidative coupling reaction, the palladation of the indole substrate proceeds via an electrophilic substitution process. As previously described, the electrophilic palladium should attack at the aromatic heterocycle's nucleophilic 3-position, followed by a 1,2-migration of the metal to the indole's 2-position (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 2-arylated indole products (compare **11** with **18**, Table 2). Consequently, we hypothesized that indole substrates bearing both electron-donating and electron-withdrawing groups were 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 energy of activation $\Delta G^{\ddagger}$) were evaluated with indoles bearing electron donating and electron withdrawing groups (Table 3). In accord with experimental outcomes, the $\Delta G^{\ddagger}$ 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 non-substituted indole (entry 2).

To explain the impact of electron donating and withdrawing groups on direct arylation reactivity of indoles, the contributions to free energy of activation $\Delta G^{\ddagger}$ were calculated using the distortion/interaction analysis of the corresponding transition states. In this approach, the distortion energy E_{dist}, associated with distortion of both the arene (ArH) and the catalyst (Pd(OAc)$_2$) from their ground state geometries to the geometries in the transitions state, and the electronic interaction energy E_{int}, between Pd(OAc)$_2$ and ArH in the CMD transition state, were evaluated (Table 3). The OMe group in the indole increases E_{dist}(ArH) by 3.0 kcal mol^{-1} (entries 1 vs 2). On the other hand, the NO$_2$ group in the indole decreases E_{dist}(ArH) by 4.7 kcal mol^{-1} (entries 3 vs 2). The 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 and withdrawing substituent was also found to influence the interaction energy E_{int} (Table 3). E_{int} becomes more negative for the indole bearing an OMe substituent and less negative for the indole bearing an NO$_2$ substituent. The analysis of the covalent interactions in the CMD transition states also indicates that the Pd−C bond order decreases in order OMe > H > NO$_2$. Since the influence of the substituents on E_{dist}(ArH) is less than their influence on E_{int}, the observed reactivity trend (OMe > H > NO$_2$) for these indole substrates is caused by a change in electronic interaction energy (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 the 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 only involve two donor orbitals (the HOMO and HOMO-1) of the indole. When the CMD transition state is formed, these two orbitals change their electron population 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 C-2 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, this orbital changes its population by 21.1%. On the other hand, 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 the E_{int} is only −45.0 kcal mol^{-1} (Table 3, entry 3), compared to E_{int} 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 electrophilic substitution or proton abstraction processes. Alternatively, the palladation of the simple arene could proceed via concerted metalation-deprotonation mechanism.20

To test these two hypothetical reaction pathways we performed a competition experiment in which the indole **34** was mixed with equimolar amounts of *ortho*-dichlorobenzene (**40**) and *ortho*-xylene **(41)** (Figure 6, reaction **a**). Our optimal conditions for oxidative cross-coupling resulted in a near equal mixture of products (1.1:1, **26**:**30**). 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 *ortho*-trifluoromethyltoluene (**42**), (Figure 6, reaction **b**). Interestingly, a 1.4:1 ratio of products (**43:44**) was observed, with the major product arising from palladation *para* to the methyl group. The results of these competition studies, in which there is no marked chemoselectivity, are neither consistent with an electrophilic palladation mechanism nor a proton abstraction mechanism involving the build-up of charged intermediates.

Computational analysis of the arene **42** provides insight into the mechanism by which it is palladated (see 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 a palladation via an S_EAr mechanism. The anion corresponding to abstraction of the position *para* to the trifluoromethyl group is more stable than that of the anion 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 are computed to be identical (1.075 Å). Previous computational and experimental work has shown the CMD mechanism is favoured 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 be easily 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 studies on the oxidative coupling reaction and varied the concentration of the PivOH (Figure 6, reaction **c**). It has been previously suggested that that electrophilic palladation processes, in which minimal C-H bond breaking is involved the transition state (KIE < 3), should be favoured by higher concentrations of acid (usually AcOH; in our case PivOH). Conversely, reactions containing less acid, should be more basic, and should favor a 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 between equimolar amounts of benzene and benzene-*d₆*, indicating that the palladation proceeded through a CMD mechanism and that the cleavage of the solvent arene's C-H bond was rate-determining. Furthermore, the data shows 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 opposed to competing electrophilic palladation and proton abstraction mechanisms.

Conclusions

The data presented in this article 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 mechanism.20 Other researchers have described similar metalation processes, which have been called proton abstraction24–26 or σ-bond metathesis,27 and numerous palladium catalyzed C-H functionalizing 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 may be operating 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 media. Rather, a given C-H bond's propensity towards participation 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 oxidatively cross-coupling indoles with benzene substrates via double C-H functionalization. Both the indole and the simple arene substrates are palladated by concerted metalation-deprotonation processes. This work represents the first example of the CMD mechanism operating in acidic reaction media, as is common for oxidative cross coupling reactions. However, we have shown that the acidity of the media does not significantly affect the CMD process for the palladation of simple, benzene-derived arenes, but does affect the regioselectivity of the palldation 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 were 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), 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 portions of 40 mL of brine followed by two portions of 40 mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and 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-NMR, ^{13}C-NMR and mass spectrometry (see supporting information for complete characterization).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

(1). McGlacken GP, Bateman LM. Chem. Soc. Rev. 2009; 38:2447. [PubMed: 19623360]

(2). Chen X, Engle K, Wang D, Yu J-Q. Angew. Chem. Int. Ed. 2009; 48:5094.

(3). Joucla L, Djakovitch L. Adv. Synth. Cat. 2009; 351:673.

(4). Li C-J. Acc. Chem. Res. 2009; 42:335. [PubMed: 19220064]

(5). Li B, Yang S, Shi Z. Synlett. 2008; 2008:949.

(6). Alberico D, Scott ME, Lautens M. Chem. Rev. 2007; 107:174. [PubMed: 17212475]

(7). Rong Y, Li R, Lu W. Organometallics. 2007; 26:4376.

(8). Brasche G, García-Fortanet, Buchwald SL. Org. Lett. 2008; 10:2207. [PubMed: 18465866]

(9). Zhao X, Yeung CS, Dong VM. J. Am. Chem. Soc. 2010; 132:5837. [PubMed: 20359220]

(10). Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer JL Jr. Linderman RJ, Lorenz K, Manley J, Pearlman BA, Wells A, Zaks A, Zhang TY. Green Chem. 2007; 9:411.

(11). Bandini M, Eichholzer A. Angew. Chem. Int. Ed. 2009; 48:9608.

(12). Sundberg, RJ. The Chemistry of Indoles. Academic Press; 1970.

(13). Dwight TA, Rue NR, Charyk D, Josselyn R, DeBoef B. Organic Letters. 2007; 9:3137. [PubMed: 17616203]

(14). Witkop B, Patrick JB, Rosenblum M. Journal of the American Chemical Society. 1951; 73:2641.

(15). Potavathri S, Dumas AS, Dwight TA, Naumiec GR, Hammann JM, DeBoef B. Tetrahedron Lett. 2008; 49:4050. [PubMed: 19652690]

(16). Stuart DR, Villemure E, Fagnou K. J. Am. Chem. Soc. 2007; 129:12072. [PubMed: 17880083]

(17). Stuart DR, Fagnou K. Science. 2007; 316:1172. [PubMed: 17525334]

(18). Liégault B, Lee D, Huestis MP, Stuart DR, Fagnou K. J. Org. Chem. 2008; 73:5022. [PubMed: 18543991]

(19). Lane BS, Brown MA, Sames D. J. Am. Chem. Soc. 2005; 127:8050. [PubMed: 15926829]

(20). Gorelsky SI, Lapointe D, Fagnou K. J. Am. Chem. Soc. 2008; 130:10848. [PubMed: 18661978]

(21). Spartan '08. Wavefunction, Inc.;

(22). Campeau L, Parisien M, Jean A, Fagnou K. J. Am. Chem. Soc. 2006; 128:581. [PubMed: 16402846]

(23). Pascual S, de Mendoza P, Echavarren AM. Org. Biomol. Chem. 2007; 5:2727. [PubMed: 17700837]

(24). García-Cuadrado D, Braga AAC, Maseras F, Echavarren AM. J. Am. Chem. Soc. 2006; 128:1066. [PubMed: 16433509]

(25). García-Cuadrado D, de Mendoza P, Braga AAC, Maseras F, Echavarren AM. J. Am. Chem. Soc. 2007; 129:6880. [PubMed: 17461585]

(26). Lafrance M, Rowley CN, Woo TK, Fagnou K. J. Am. Chem. Soc. 2006; 128:8754. [PubMed: 16819868]

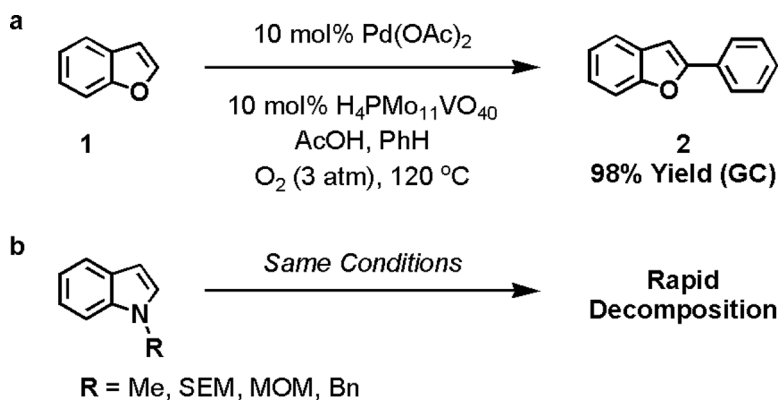(27). Hull KL, Sanford MS. J. Am. Chem. Soc. 2009; 131:9651. [PubMed: 19569623]

a

10 mol% Pd(OAc)$_2$

10 mol% H$_4$PMo$_{11}$VO$_{40}$

AcOH, PhH

O$_2$ (3 atm), 120 °C

1

2

98% Yield (GC)

b

Same Conditions

Rapid
Decomposition

R = Me, SEM, MOM, Bn

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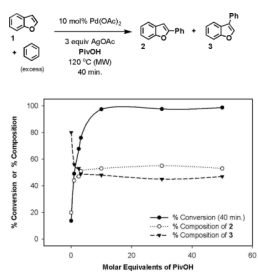MOM = methoxymethyl, Bn = benzyl)

Figure 2.
Oxidative coupling of benzofuran (**1**) and benzene as a function of acid concentration
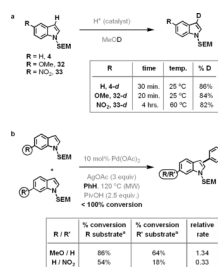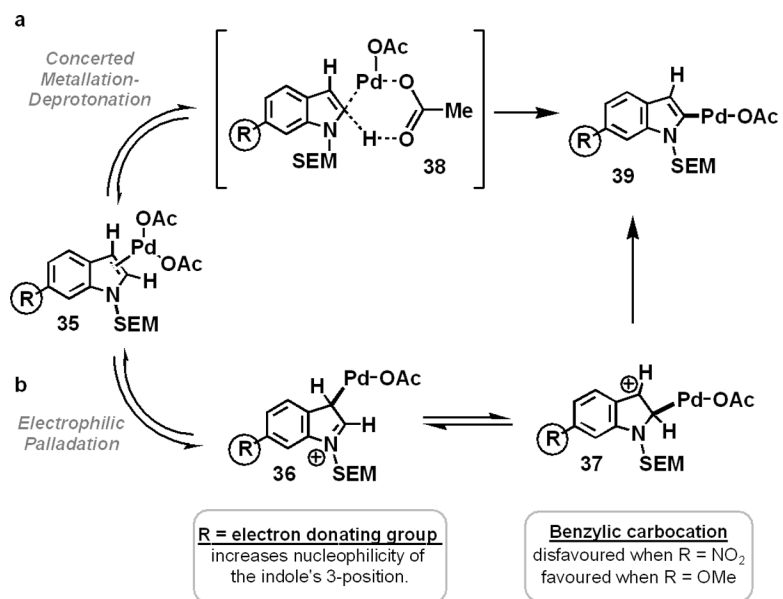
Figure 3.
Probing the mechanism of indole palladation

Figure 4.
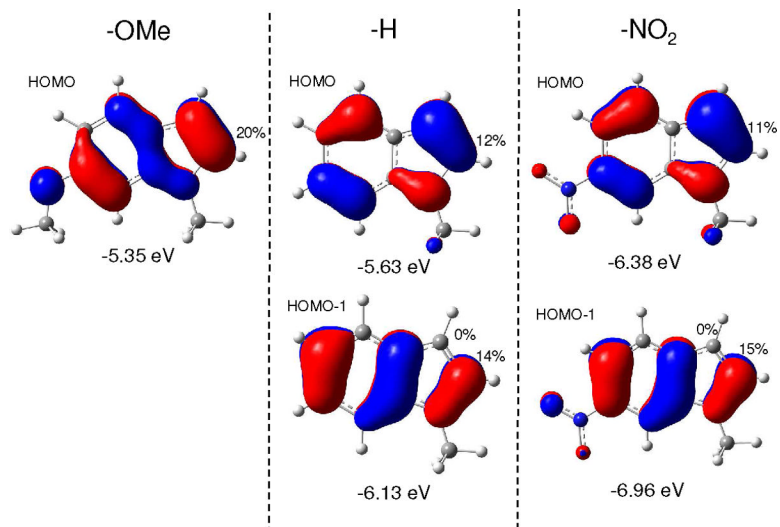Potential mechanisms for palladating indole

Figure 5.
The occupied frontier orbitals for the indoles that contribute to the interaction with the Pd(II) catalyst in the CMD transition state. The C-2 atomic contribution (%) and the energy (eV) for each orbital are shown
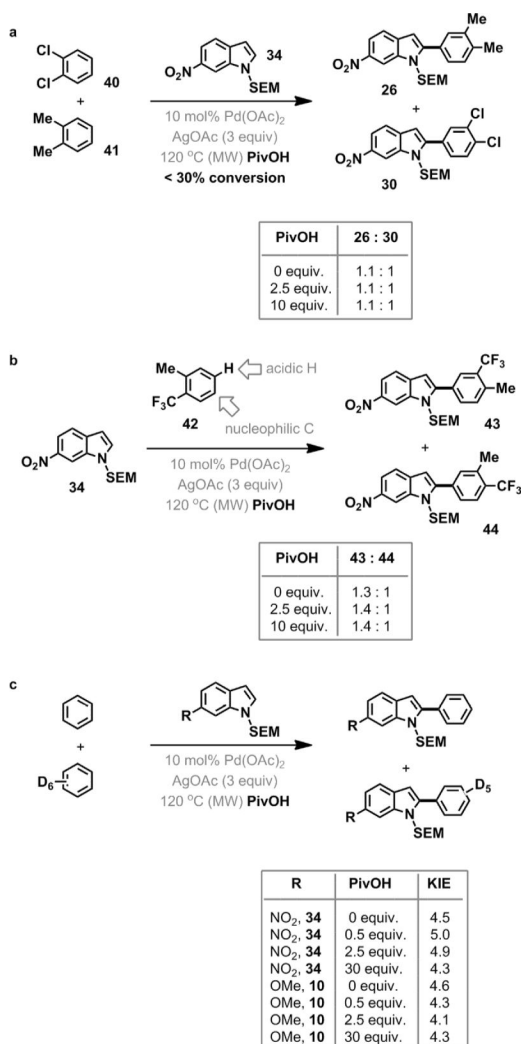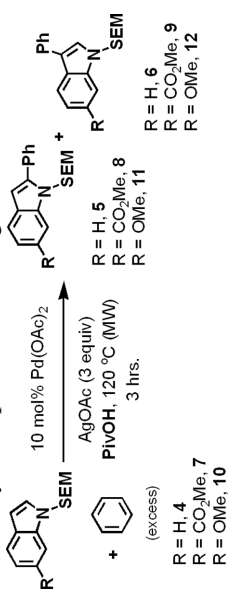
Figure 6.
Probing the mechanism of palladation of the simple arene substrate

Table 1

Discovery and optimization of regioselective oxidative arylation with electron-rich indoles

Entry	R	PivOH	Conv.[a]	Yield[a]	Ratio[b]
1	H	0 equiv	62%	43%	2.1:1
2	H	1 equiv	81%	58%	2.2:1
3	H	2.5 equiv	96%	69%	2.6:1
4	H	5 equiv	98%	65%	2.5:1
5	CO2Me	2.5 equiv	100%	97%	8.7:1
6	OMe	2.5 equiv	100%	56%	2.7:1

[a] Unreacted starting material and products were isolated by flash chromatography.

[b] **5:6**, **8:9** and **11:12** determined by GC.

Table 2

Scope of oxidative arylation reaction*a*

Variation of *N*-Substituent*b*

Variation of Indole Substrate*b*

8 97% yield (9:1)	**18** 88% yield *only isomer*	**19** 77% yield (28:1)
20 73% yield (13:1)	**21** 67% yield (4:1)	**22** 72% yield (8:1)
11 56% yield (3:1)	**23** 48% yield (4:1)	**24** 61% yield (3:1)

Variation of Benzene Substrate*b*
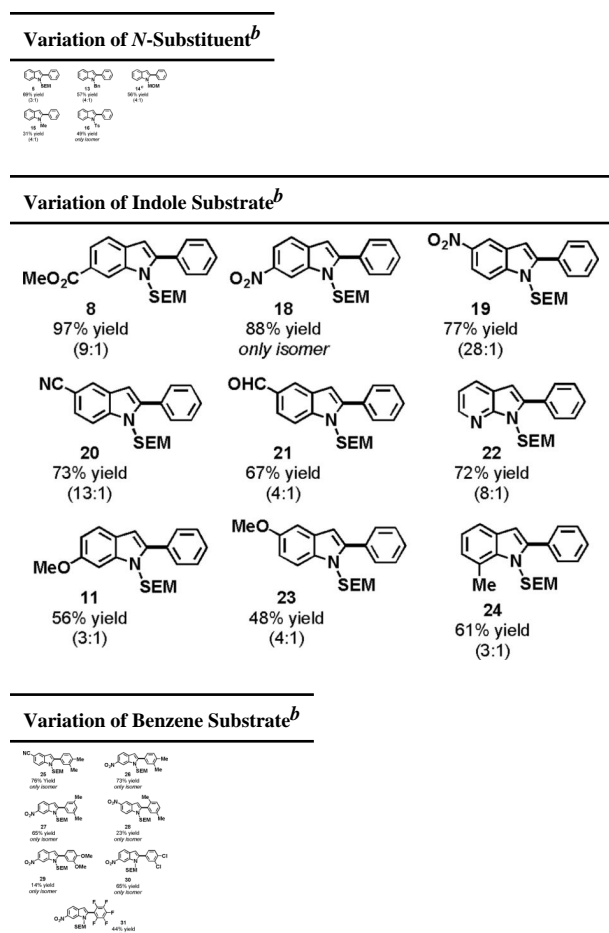
*a*0.15 mmol indole, 4 mL arene, 10 mol % Pd(OAc)$_2$, 3 equiv AgOAc, 2.5 equiv PivOH, 120 °C (MW).

*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.

Table 3

Distortion/interaction analysis (kcal mol^{-1}) for the lowest free energy CMD transition states at the C–2 sites of N-methylindoles bearing electron donating and withdrawing groups on their 6-positions

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 Pd-C$_{Ar}$ interaction in the TS.