Catalyst-Controlled Regioselectivity in Pd-Catalyzed Aerobic Oxidative Arylation of Indoles

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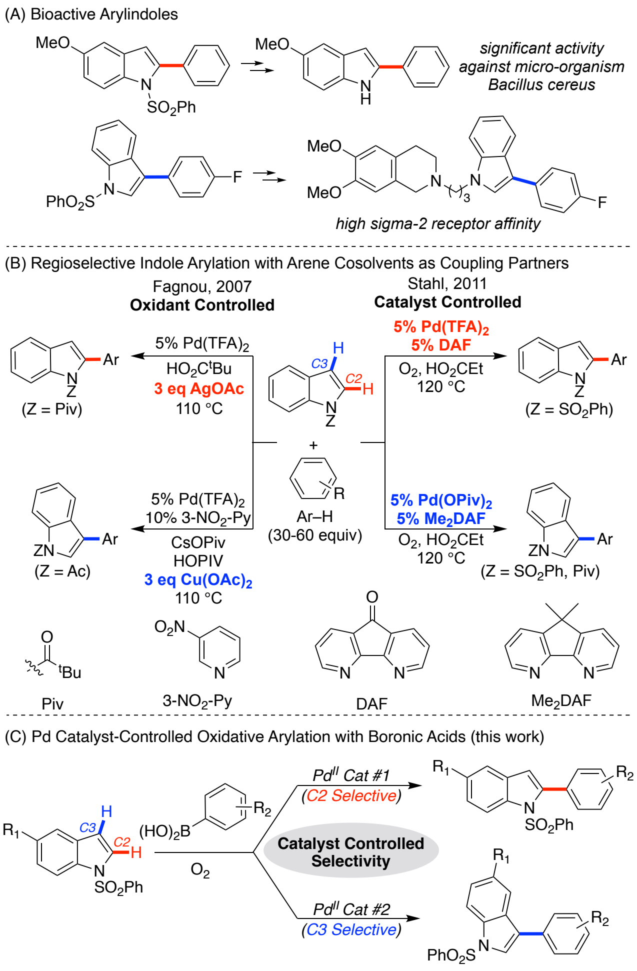
ABSTRACT: Pd-catalyzed C–H arylation of heteroarenes is an important and widely studied synthetic transformation; however, the regioselectivity is often substrate-controlled. Here, we report catalyst-controlled regioselectivity in the Pd-catalyzed oxidative coupling of *N*-(phenylsulfonyl)indoles and aryl boronic acids using O_2 as the oxidant. Both C2- and C3-arylated indoles are obtained in good yield with >10:1 selectivity. A switch from C2 to C3 regioselectivity is achieved by including 4,5-diazafluoren-9-one or 2,2'-bipyrimidine as an ancillary ligand to a "ligand-free" $Pd(OTs)_2$ catalyst system. Density functional theory calculations indicate that the switch in selectivity arises from a change in the mechanism, from a C2-selective oxidative-Heck pathway to a C3-selective C–H activation/reductive elimination pathway.

Oxidative arylation of (hetero)aromatic C–H bonds provide efficient access to biaryl compounds; however, these reactions can lead to a mixture of regioisomers when more than one reactive C–H bond is present in the substrate.[1-3] In some cases, substrates react preferentially at a single C–H site,[4,5] while, in other cases, directing groups guide the catalyst to a desired site.[6] Ideally, site selectivity could be achieved via catalyst control, without requiring a directing group in the substrate.[7] Reactions of indoles have been the focus of extensive attention, and C2- and C3-aryl derivatives are prominently featured in biologically active molecules (e.g., Scheme 1A[8,9]). Synthetic methods have been developed to access either C2 or C3 site-selectivity,[10-12] using oxidative and non-oxidative C–H arylation methods.[13-28] Seminal studies by Fagnou[14,15] and DeBoef[16,17] demonstrated Pd-catalyzed oxidative C–H/C–H coupling of indoles with simple arenes. A switch in regioselectivity was achieved by changing the reaction conditions, most notably by changing the stoichiometric oxidant from AgOAc (C2 selective) to $Cu(OAc)_2$ (C3 selective) (Scheme 1B, left).[29-31] We later showed that analogous arylation reactivity could be achieved with O_2 as the oxidant, with regioselectivity controlled by the identity of the neutral and anionic Pd ligands (Scheme 1B, right).[20]

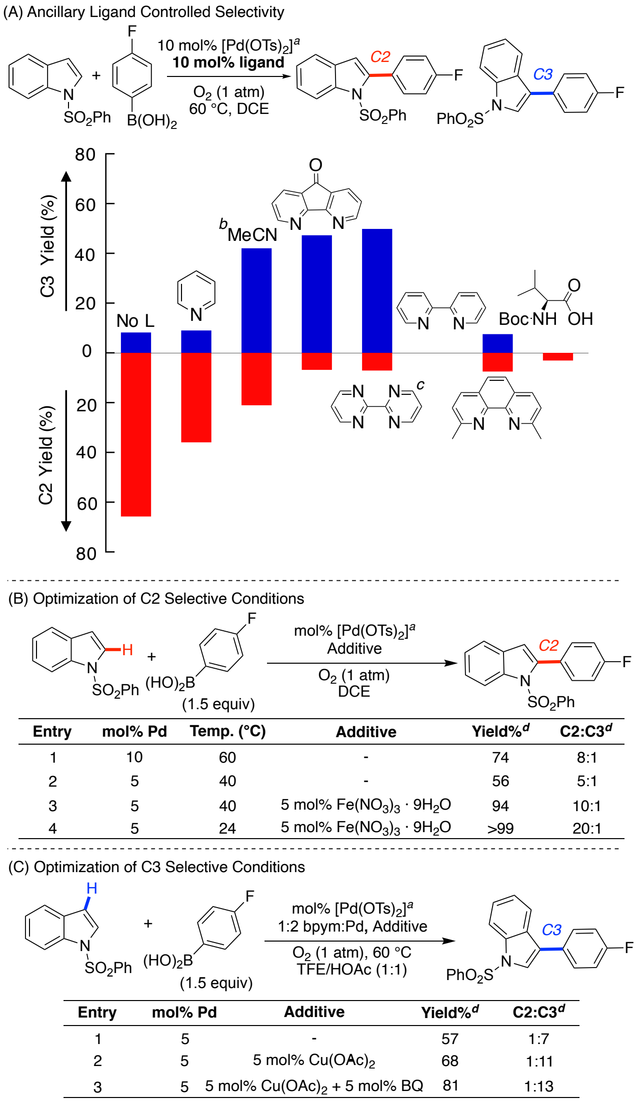
Pd-catalyzed oxidative arylation of indoles with boronic acids represents an alternative route to these products, incorporating several synthetically appealing features. They operate under mild conditions, employ approximately 1:1 substrate ratios, and exhibit broad scope with respect to the aryl coupling partner. Previous examples of these reactions exhibit nearly exclusive selectivity for arylation at the C2 position.[8,18,32-36] In the present study, we demonstrate aerobic oxidative coupling of arylboronic acids with *N*-(phenylsulfonyl)indoles and show that either C2 or C3 selectivity is possible, depending on the catalyst identity (Scheme 1C).[37-39] Selective C2-arylation is observed with an electrophilic $Pd(OTs)_2$ catalyst, while high C3 selectivity is observed upon addition of 4,5-diazafluoren-9-one (DAF) or 2,2'-bipyrimidine (bpym) as an ancillary ligand. Insights from density functional theory (DFT) calculations show that this change in selectivity arises from ligand-based inhibition of an oxidative-Heck arylation mechanism, which favors C2 selectivity. In the presence of the chelating ligand, a C3-selective C–H activation/reductive elimination pathway is favored.

Scheme 1. Purpose and Goal for Catalyst-Controlled Selective Aerobic Arylation of *N*-(Phenylsulfonyl)Indoles



N-(Phenylsulfonyl)indole and 4-fluorophenylboronic acid were selected as the initial substrate partners owing to their relevance to the bioactive molecules in Scheme 1A.[8,9] The $Pd(OAc)_2$/AcOH conditions similar to those used for arylation of electron-rich *N*-

H/alkyl indoles showed poor reactivity with the *N*-(phenylsulfonyl)indole.[18] Changing the solvent to 1,2-dichloroethane (DCE) and replacing the acetates with non-basic anionic ligands had a beneficial effect.[40] In particular, $Pd(OTs)_2$ (Ts = 4-toluenesulfonyl), generated *in situ* by adding 4 equiv TsOH to $Pd(OAc)_2$, catalyzed the desired arylation reaction in 74% yield with an 8:1 C2:C3 product ratio (Figure 1A - No L). Addition of ancillary ligands had mixed results. Addition of 1 equiv of pyridine to the $Pd(OTs)_2$ catalyst diminishes the yield and selectivity (45%, C2:C3 = 4:1) system, while addition of 2 equiv of acetonitrile leads to an improved yield and a switch in selectivity (63%, C2:C3 = 1:2). Mono-*N*-protected amino acids (MPAAs)[41] and many bidentate ligands (e.g., 2,2'-bipyridine, neocuproine) inhibit or fail to improve yields or selectivity (Figure 1A); however, two exceptions were identified: 4,5-diazafluoren-9-one (DAF) and 2,2'-bipyrimidine (bpym), both of which supported good reactivity and C3 selectivity (Figure 1A).



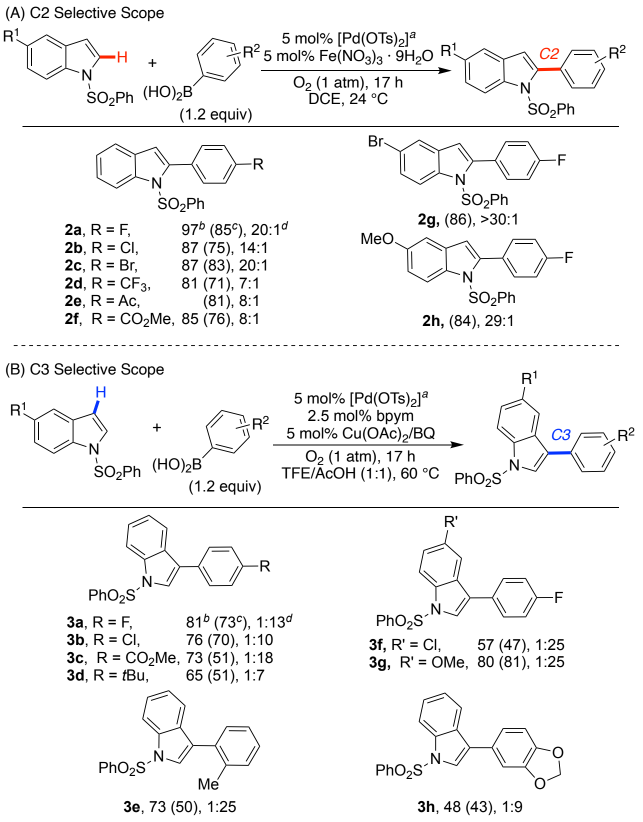
Entry	mol% Pd	Temp. (°C)	Additive	Yield%[d]	C2:C3[d]
1	10	60	-	74	8:1
2	5	40	-	56	5:1
3	5	40	5 mol% $Fe(NO_3)_3 \cdot 9H_2O$	94	10:1
4	5	24	5 mol% $Fe(NO_3)_3 \cdot 9H_2O$	>99	20:1

Entry	mol% Pd	Additive	Yield%[d]	C2:C3[d]
1	5	-	57	1:7
2	5	5 mol% $Cu(OAc)_2$	68	1:11
3	5	5 mol% $Cu(OAc)_2$ + 5 mol% BQ	81	1:13

Figure 1. Ligand effects on yield and regioselectivity in the coupling of *N*-(phenylsulfonyl)indole and 4-fluorophenylboronic acid (A) and selected optimization data for of C2 selective (B) C3 selective (C) arylation reactivity. Conditions beyond those indicated in the graphic: Indole (0.2 mmol), 17 h, 1 mL solvent. [a]$Pd(OTs)_2$ generated in-situ from $Pd(OAc)_2$ and $TsOH{\cdot}H_2O$ (1:4). [b]$(MeCN)_2Pd(OTs)_2$ was used as the catalyst with no additional ligand [c]The reaction with 2,2'-bipyrimidine was performed with 5% $[Pd(OTs)_2]$ and 2.5% ligand in acetic acid/trifluoroethanol (1:1) as the solvent. [d]Determined by ^1H NMR analysis (int. std. = 1,1,2,2-tetrachloroethane).

Building on this initial survey, we further optimized the catalyst systems and reaction conditions to access the C2- and C3-arylation products, targeting higher yields and selectivities. The Pd loading was lowered to 5 mol%, and selected data leading to the optimal conditions are shown in Figures 1B and 1C (see Tables S1 and S2 of the Supporting Information for full screening data). Assessment of various transition metal and Lewis acid cocatalysts showed that inclusion of 5 mol% $Fe(NO_3)_3$ supported formation of the C2-arylation product in near quantitative yield at room temperature with a 20:1 C2:C3 selectivity (Figure 1B, entry 4). Optimization efforts for C3 arylation focused on a bpym/$Pd(OTs)_2$ catalyst system. Screening results showed that the yield and selectivity benefitted from use of a protic solvent mixture (AcOH/tri-fluoroethanol) and a somewhat higher reaction temperature (60 °C; Figure 1C). Optimal conditions featured the use of $Cu(OAc)_2$ and benzoquinone (BQ) as cocatalysts, resulting in full conversion of the starting material and an 81% product yield with a C2:C3 selectivity of 1:13 (Figure 1C, entry 3).

This ability to achieve catalyst-controlled regioselectivity in the oxidative arylation of *N*-(phenylsulfonyl)indoles proved effective with other substrates (Figure 2). The two catalyst systems consist of $Pd(OTs)_2/Fe(NO_3)_3$ for C2-selective arylation and $Pd(OTs)_2$/bpym/Cu^{II}/BQ for C3-selective arylation, both using 5% Pd loading and 1 atm O_2 as stoichiometric oxidant. Good yields are



2a, R = F, 97^b (85^c), $20{:}1^d$
2b, R = Cl, 87 (75), 14:1
2c, R = Br, 87 (83), 20:1
2d, R = CF_3, 81 (71), 7:1
2e, R = Ac, (81), 8:1
2f, R = CO_2Me, 85 (76), 8:1
2g, (86), >30:1
2h, (84), 29:1

3a, R = F, 81^b (73^c), $1{:}13^d$
3b, R = Cl, 76 (70), 1:10
3c, R = CO_2Me, 73 (51), 1:18
3d, R = *t*Bu, 65 (51), 1:7
3f, R' = Cl, 57 (47), 1:25
3g, R' = OMe, 80 (81), 1:25
3e, 73 (50), 1:25
3h, 48 (43), 1:9

Figure 2. Substrate scope for the C2 (A) and C3 (B) selective arylation methods. Conditions: (A,B) See schemes, indole (0.2 mmol), 17 h, 1 mL solvent. [a]$Pd(OTs)_2$ generated in-situ from $Pd(OAc)_2$ and $TsOH{\cdot}H_2O$ (1:4 for C2 conditions and 1:8 for C3 conditions). [b]NMR yields determined by ^1H NMR analysis (int. std. = 1,1,2,2-tetrachloroethane). [c]Isolated yields (obtained as a mixture of regioisomers in the indicated ratio). [d]Regioselectivities determined by ^1H NMR analysis.

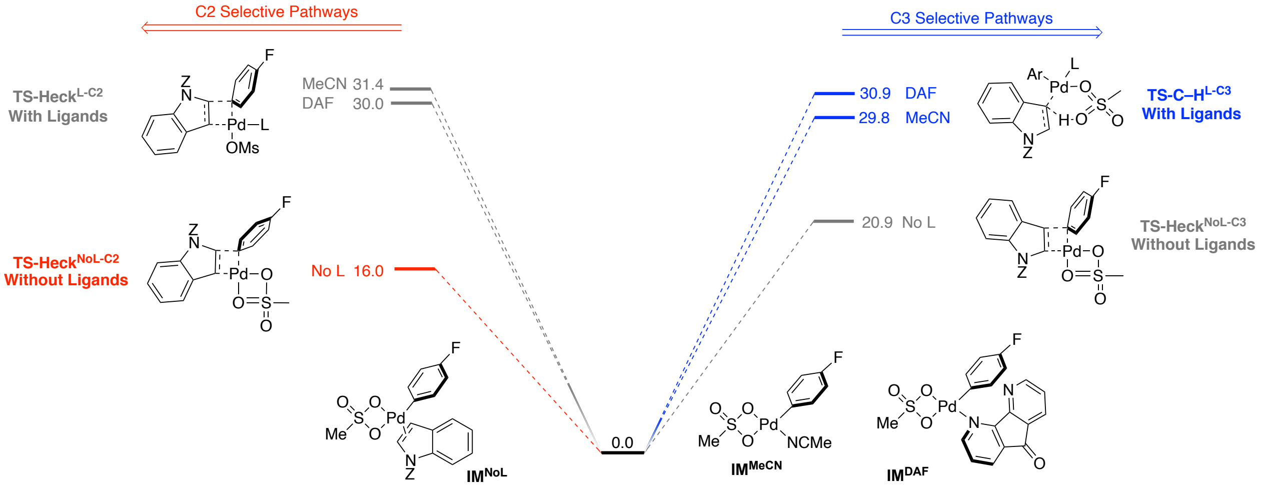


Figure 3. Computational results probing the switch in selectivity by use of ancillary ligands. -Z = $-SO_2Ph$, Unit: kcal/mol. See text and the Supporting Information Section 5 for computational details.

accessible with several different *N*-(phenylsulfonyl)indoles and with boronic acids bearing various substituents, including halides amenable to further derivatization. Good-to-excellent regioselectivity was observed in each of the cases shown; however, electron-rich arylboronic acids appear to be susceptible to side-product formation.[42]

Among methods available to access C2- and C3-arylindoles,[13-28] the reactions described here provide a unique opportunity to probe the mechanistic origin of catalyst-controlled regioselectivity. Aryl transmetalation from boron to Pd^{II} under aerobic conditions similar to those used here is facile, often proceeding efficiently at room temperature.[43-46] The $L_nPd(Ar)X$ species generated in this step could then react with indole to afford the desired coupling product. At least two different pathways could be considered for this C–C coupling step: (a) a Heck-type pathway initiated by insertion of the indole C2-C3 double bond into a Pd–Ar bond,[28] or (b) indole C–H activation by Pd^{II}, followed by C–C reductive elimination.[47] Studies of thiophene arylation with aryl halides suggest that both Heck and C–H activation pathways are possible,[48-50] and we postulated that our observed switch in regioselectivity could arise from a change in the preferred mechanism under different conditions.

The relative energetics of these two pathways were probed computationally, focusing on the reaction of a $Pd(Ar)(O_3SMe)$ fragment with *N*-phenylsufonylindole, in the absence and presence of an ancillary ligand. DFT calculations were conducted at the B3LYP-D3(BJ)/[6-311+G (d,p) + RSC 1997 ECP[51,52] (Pd)] level of theory. 1,2-Dichloroethane was chosen as the solvent using the polarizable-continuum model (PCM). The experimental tosylate anions were replace with methanesulfonate (MsO^-) to lower computational costs, and we elected to use DAF rather than bpym as an ancillary ligand, due to the similar effect of DAF and bpym on regioselectivity and our prior computational experience with DAF/Pd^{II} systems[53,54] (cf. Figure 1A). MeCN was also evaluated as an ancillary ligand.

The structures of the $Pd(Ar)(O_3SMe)$ species with and without an ancillary ligand (**IM^{MeCN}**, **IM^{DAF}**, and **IM^{NoL}**) were optimized. These species were defined as the starting energies (i.e., 0.0 kcal/mol) for energetic comparison of C2- and C3-arylindole product formation via the Heck and C–H activation mechanisms (Figure 3 and Figure S1). Significant observations from the computational results may be summarized as follows. In the absence of an ancillary ligand, the Heck pathway exhibits a relatively low barrier, with regioselectivity favoring C2 arylation (16.0 vs 20.9 kcal/mol). Barriers for the Heck pathway are significantly higher upon coordination of DAF or MeCN as an ancillary ligand: ≥30.0 kcal/mol for the C2 pathway (**TS-Heck$^{L\text{-}C2}$**; Figure 3) and ≥34.4 kcal/mol for the C3 pathway (**TS-Heck$^{L\text{-}C3}$**; Figure S1 in the Supporting Information). With a coordinated MeCN or DAF ligand, the barrier for C–H activation at the C3 position is comparable to that of the Heck pathway (Figure 3; $\Delta\Delta G^\ddagger = +0.9$ kcal/mol **TS-C–H$^{DAF\text{-}C3}$** vs **TS-Heck$^{DAF\text{-}C2}$** and $\Delta\Delta G^\ddagger = -1.6$ kcal/mol **TS-C–H$^{MeCN\text{-}C3}$** vs **TS-Heck$^{MeCN\text{-}C2}$**). In addition, C–H activation at C3 is favored over activation at C2 by 2.1 kcal/mol with both ligands (Figure S1, **TS-C–H$^{L\text{-}C3}$** vs **TS-C–H$^{L\text{-}C2}$**). While these differences are within the uncertainties of the DFT calculations, the relative energies of the C2 and C3 C–H activation energies is expected to be meaningful (i.e., C–H activation favors the C3 position).

Collectively, these observations provide a rationale for the ligand-induced switch in site-selectivity for indole arylation. C2-selective arylation appears to be accessible via a low-barrier Heck-type pathway in the absence of added ligands, while the C3-selective arylation in the presence of added ligands is rationalized by a change in mechanism, whereby C–H activation is favored at C3 over C2. The computations are consistent with mild, room-temperature reaction conditions used to access the C2-arylation product (see Figure 2). Similarly, the higher barriers computed for the C3-arylation pathway is consistent with the higher temperatures required to access the C3 products.

In conclusion, we have identified aerobic oxidation conditions that allow for catalyst-controlled regioselectivity in the arylation of indoles. C2 selectivity is accessed with a "ligand-free" Pd catalyst system, while C3 selectivity is favored with a ligated catalyst system (ligand = MeCN, DAF or bpym). Computational studies indicate that the change in selectivity arises from a change in mechanism, from a C2-selective Heck-type pathway in the absence of ligands to a C3-selective C–H activation pathway in the presence of ligands. These results, which complement insights obtained previously from reactions of thiophenes, established an important foundation for rational design of new regioselective heterocycle functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website.

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ACKNOWLEDGMENT

We thank Dr. Andrei Iosub and Dr. Alastair Lennox for helpful discussion. This project was initiated with financial support from the NSF CCI Center for Selective C–H Functionalization (CHE-1205646) and completed with support from the NSF (CHE-1953926). This material is based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. DGE-1747503 (C.A.S). Spectroscopic instrumentation was supported by a gift from Paul J. Bender, the NSF (CHE-1048642), and the NIH (1S10 OD020022-1). Computational resources were supported in part by the NSF (CHE-0840494).

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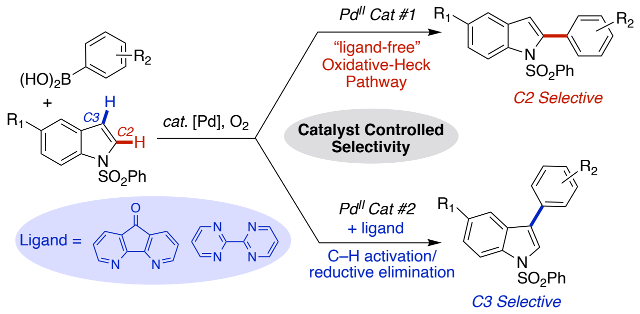
TOC Graphic


(HO)$_2$B
R$_2$
+
R$_1$
C3
H
C2
H
N
SO$_2$Ph
cat. [Pd], O$_2$
Ligand =
O
N
N
N
N
N
N
Pd^{II} Cat #1
"ligand-free"
Oxidative-Heck
Pathway
R$_1$
N
SO$_2$Ph
R$_2$
C2 Selective
Catalyst Controlled
Selectivity
Pd^{II} Cat #2
+ ligand
C–H activation/
reductive elimination
R$_1$
R$_2$
N
SO$_2$Ph
C3 Selective