

Published in final edited form as:

Chem Commun (Camb). 2011 October 7; 47(37): 10257–10259. doi:10.1039/c1cc13632a.

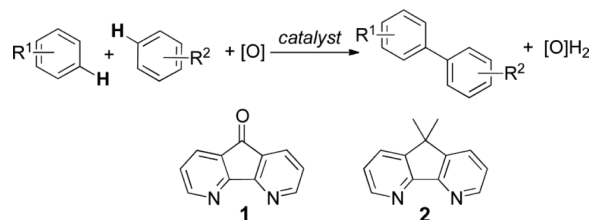
Regiocontrolled aerobic oxidative coupling of indoles and benzene using Pd catalysts with 4,5-diazafluorene ligands

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Abstract

Palladium-catalyzed aerobic oxidative cross-couplings of indoles and benzene have been achieved by using 4,5-diazafluorene derivatives as ancillary ligands. Proper choice of the neutral and anionic ligands enables control over the reaction regioselectivity.

Biaryls are an important structural motif ubiquitous in diverse classes of organic molecules, including pharmaceuticals, organic dyes, agrochemicals and conducting polymers.¹ In recent years, considerable attention has focused on the development of methods for arylation of arene C–H bonds.² The direct oxidative coupling of two arenes (eqn 1) is among the most attractive synthetic routes to biaryls,^{2h,3} but such methods face numerous intrinsic challenges, including controlling the regioselectivity in the functionalization of substituted (hetero)arenes, achieving selective cross- vs. homocoupling of the substrates, and identification of an atom-economical oxidant for the reaction. Here, we show that use of the diazafluorene derivatives, 4,5-diazafluoren-9-one (**1**) and 9,9-dimethyl-4,5-diazafluorene (**2**), as ancillary ligands for a Pd^{II} catalyst enables aerobic oxidative cross-coupling of indoles with benzene, with selectivity for C2 and C3 indole-arylation products.



(1)

The majority of Pd-catalyzed methods for oxidative cross-coupling of (hetero)arenes employ stoichiometric organic or transition-metal oxidants, such as benzoquinone (BQ), Ag^I, or

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[†]Electronic Supplementary Information (ESI) available: Reaction optimization details, characterization data and NMR spectra of characterized compounds. See DOI: 10.1039/b000000x/

[‡]General procedure for catalytic reactions: A pressure tube fitted with a plunger valve was charged with Pd (0.030 mmol), ligand (0.030 mmol), indole (0.60 mmol), EtCO₂H (270 μL, 3.6 mmol) and arene (39.6 mmol). The tube was evacuated and backfilled with O₂ (3×), sealed and heated to 120 °C for 24h with vigorous stirring. The reaction mixture was then cooled to room temperature, diluted with EtOAc and washed with sat'd. NaHCO₃. The organic layer was separated and the aqueous layer washed with EtOAc (2×). The combined organics were dried over MgSO₄, filtered and concentrated by rotatory evaporation. The crude product was purified by silica gel column chromatography (Et₂O in hexanes) to yield the cross-coupled product as a mixture of two isomers.

Cu^{II}.³ Replacement of these oxidants with O₂ represents a significant fundamental challenge that has important implications for practical applications of these methods;^{4,5} however, only limited success has been achieved thus far.⁶ Several observations suggest that the role of the oxidant in these reactions is not limited to reoxidation of these Pd⁰.⁷ For example, oxidants have been shown to promote C–C reductive elimination from Pd(II)⁸ and to control the regioselectivity of oxidative cross-coupling reactions.^{3a-d,9} In 2007, Fagnou and co-workers reported Pd-catalyzed oxidative cross-coupling of indoles with benzene in which they demonstrated selective functionalization of the indole C3 position when Cu(OAc)₂ was used as the oxidant,^{3a} but C2 selectivity with AgOAc as the oxidant (Scheme 1A).^{3b} These observations provide the foundation for the present investigation.

We demonstrated recently that the diazafluorenone ligand **1** promotes acetoxylation of π -allyl-Pd^{II} species, enabling benzoquinone to be replaced by O₂ as the oxidant in Pd-catalyzed allylic C–H acetoxylation reactions.¹⁰ This result prompted us to consider whether analogous ligand-based strategies could be used to achieve oxidative cross-coupling of (hetero)arenes with O₂ as the oxidant, preferably with control over the reaction regioselectivity (Scheme 1B).

In the present study, we focused our attention on the oxidative coupling of indoles and benzene. A number of different nitrogen ligands, including pyridine, phenanthroline and related derivatives were evaluated in reaction of *N*-pivalyl indole with benzene. The reactions were carried out with 5 mol % of a Pd^{II} source at 120 °C under 1 atm of O₂. Benzene served as the substrate and as a cosolvent with pivalic acid (Table 1). Reactions with pyridine and 2-fluoropyridine¹¹ exhibited modest yields (~20–30%), while reactions with bipyridine, phenanthroline and related bidentate ligands (entries 4–11) showed little product formation. Use of diazafluorenone derivatives **1** and **2** gave the best results, with 45% and 66% product yields, respectively.

The reaction was further optimized by examining the effect of indole *N*-substituent and the acid additive on the yield and regioselectivity (Table 2). The highest product yields and regioselectivities were obtained with the *N*-benzenesulfonyl (SO₂Ph) group and propionic acid (Table 2, entry 4). More extensive screening data is provided in the ESI.

Several different Pd^{II} sources were examined in the course of these studies, and the identity of the anionic ligand was found to have a strong effect on the reaction regioselectivity. These observations resemble results noted recently by Sanford et al. in BQ-promoted oxidative coupling reactions.^{8d} Trifluoroacetate favors the formation of the C3-functionalized product, while pivalate in combination with **2** led to almost no regioselectivity (Table 2, entry 6). When Pd(OPiv)₂ was used with the diazafluorenone ligand **1**, a switch in regioselectivity was observed, favoring the C2-functionalized product (Table 2, entry 9). The addition of CsOPiv (20 mol%) to the standard reaction mixture led to a similar increase in the formation of C2-arylated products.¹² The yield of biphenyl was not rigorously quantified in each case, but it was generally $\leq 20\%$.

These observations demonstrate that regioselective aerobic oxidative coupling of indoles can be achieved by proper selection of the anionic and neutral ligands for the Pd catalyst. Catalyst system A, with Pd(TFA)₂, and ligand **2**, favors the C3-functionalized product; and catalyst system B, with Pd(OPiv)₂, with **1**, favors the C2-functionalized product. These insights were then applied to a small series of other indole substrates (Table 3). The *N*-pivalyl indole gave superior selectivity under the conditions optimized for the C2 product (entry 1) while the *N*-benzenesulfonyl indole showed higher regioselectivity under the C3 optimized conditions (entry 2). The 5- and 6-substituted chloro and methoxy derivatives were used to probe the influence of electron-withdrawing and electron-donating groups on

the reaction outcome. Neither substituent had a significant impact on the yields, but the regioselectivity varied (Table 3, entries 3–6). With the Pd(TFA)₂/2 catalyst system (A) the presence of an electron-donating or -withdrawing group in either position led to a deterioration of the regioselectivity. However, with the Pd(OPiv)₂/1 catalyst system (B), the regioselectivity was improved by the presence of an electron-withdrawing group in the 5- or 6-positions.

Overall, these observations establish that diazafluorene-derived ancillary ligands enable the replacement of stoichiometric transition metals with O₂ as the oxidant in Pd-catalyzed oxidative cross-coupling of (hetero)arenes. Moreover, optimization of the neutral and anionic ligands permits control over the regioselectivity of the reactions.

The mechanistic basis for these results is not yet understood, but at least two general mechanisms can be considered.¹³ One involves sequential activation of the indole and benzene at a single Pd^{II} center, followed by reductive elimination of the product and reoxidation of Pd⁰ by O₂. An alternative pathway involves activation of indole and benzene at independent Pd^{II} centers, followed by transmetalation to afford the Pd^{II}(phenyl)(indolyl) intermediate that undergoes reductive elimination of the product. Distinguishing between these possibilities and exploring the basis for the reaction regioselectivity will be an important focus of future work.

A few preliminary mechanistic observations can be noted. When reactions with catalysts A and B were carried out with a 1:1 mixture of C₆H₆ and C₆D₆, deuterium kinetic isotope and effects varied from 2.8–3.8, depending upon the specific reaction¹². This primary KIE is consistent with a concerted metalation-deprotonation pathway for C–H activation that has been characterized previously in related reactions¹⁴. When the reaction was carried out with CD₃CO₂D as the acid additive, extensive deuterium incorporation was observed into the benzene and the indole substrates. Deuteration of the indole ring occurred primarily at the C3-position, irrespective of the catalyst system, even though catalyst B leads to predominant C2-functionalization. Negligible deuteration occurs in the absence of Pd^{II} under these conditions.¹² These results, which indicate that C–H activation is reversible for both substrates under the reaction conditions, potentially provide circumstantial support for a transmetalation mechanism, but more work is required before a conclusion can be reached. The relative simplicity of the catalyst systems should facilitate such mechanistic investigations.

We thank Paul White (UW-Madison) for experimental assistance, and we are grateful to the NIH (R01-GM67163/SSS; F32-GM087890/ANC) and the Camille and Henry Dreyfus Postdoctoral Program in Environmental Chemistry for financial support of this work. High-pressure instrumentation was supported by the NSF (CHE-0946901).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

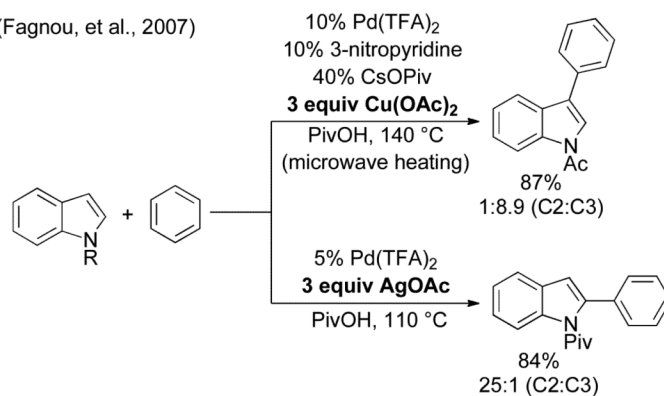
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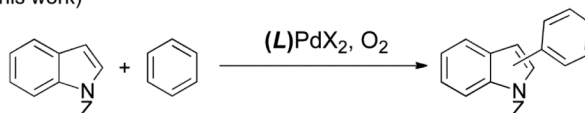
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A) Precedent: Oxidant-Controlled Regioselectivity

(Fagnou, et al., 2007)

**B) Target: Catalyst-Controlled Regioselectivity with O₂ as the Oxidant**

(This work)

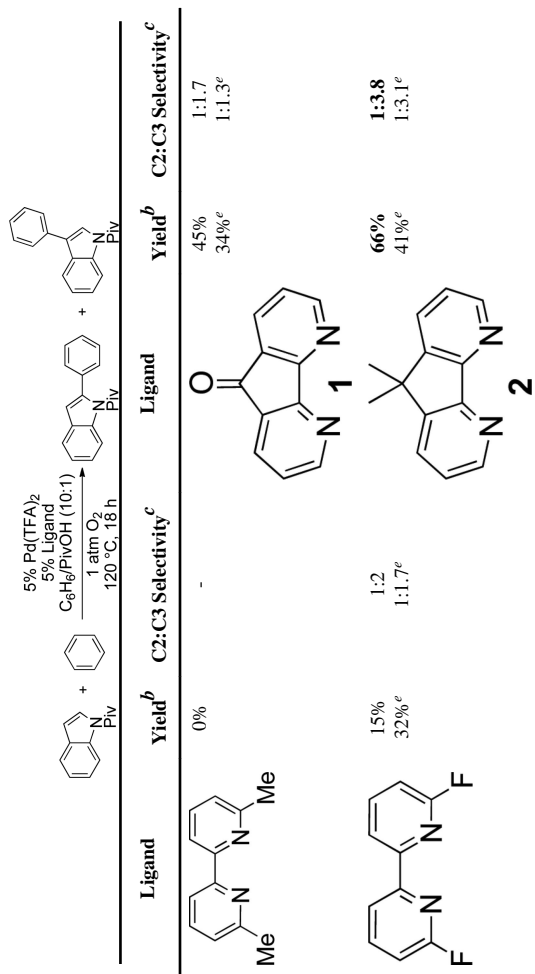


Scheme 1.
Oxidant-Controlled Regioselectivity.

Table 1

Identification of a ligand for palladium-catalyzed aerobic oxidative cross-coupling^a

Ligand	Yield ^b	C2:C3 Selectivity ^c	Ligand	Yield ^b	C2:C3 Selectivity ^c
None	15%	1:1		10%	1:1
	22% ^d	1:1		0%	-
	18% ^d	1.6:1 ^d			
	24% ^d	1:1.4		14%	1:2.5
	29% ^d	1.9:1 ^d		14%	1:1.3
	31% ^d	2.4:1		9%	1:2
	47% ^d	2.9:1 ^d		0%	-
	0%	-		9%	1:1 ^e
	9% ^e	1:1 ^e		0%	-



^a Conditions: 5% Pd(TFA)₂ (7.5 μmol), 5% ligand (7.5 μmol), indole (0.15 mmol), PivOH (0.90 mmol), benzene (9.9 mmol), 1 atm O₂, 120 °C, 18h.

^b By ¹H NMR (internal standard = tetrachloroethane).


^c Determined by ¹H NMR.

^d 10% ligand.

^e 2.5% ligand

Table 2

Identification of optimized conditions for palladium-catalyzed oxidative coupling of indoles with benzene^a



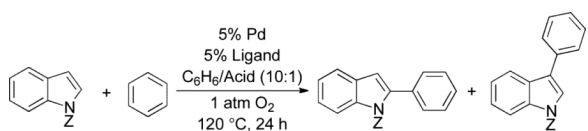
Entry	Z	Acid	Catalyst	Ligand	Yield ^b	C2:C3 Selectivity ^c
1	Piv	PivOH	Pd(TFA) ₂	2	66%	1:3.8
2	Ac	PivOH	Pd(TFA) ₂	2	67%	1:1.2
3	SO ₂ Ph	PivOH	Pd(TFA) ₂	2	77%	1:5
4	SO₂Ph	EtCO₂H	Pd(TFA)₂	2	89%	1:5.8
5	SO ₂ Ph	EtCO ₂ H	Pd(OAc) ₂	2	63%	1:2.2
6	SO ₂ Ph	EtCO ₂ H	Pd(OPiv) ₂	2	68%	1:1.5
7	SO ₂ Ph	EtCO ₂ H	Pd(TFA) ₂	1	64%	1:4.8
8	SO ₂ Ph	EtCO ₂ H	Pd(OAc) ₂	1	85%	1.4:1
9	SO₂Ph	EtCO₂H	Pd(OPiv)₂	1	80%	2:1

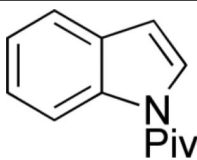
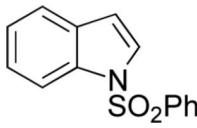
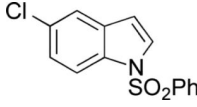
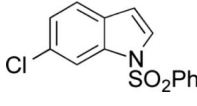
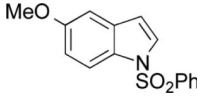
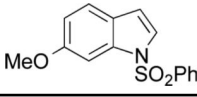
^a Conditions: 5% Pd (7.5 μmol), 5% ligand (7.5 μmol), indole (0.15 mmol), acid (0.9 mmol), benzene (9.9 mmol), 1 atm O₂, 120 °C, 18h.

^b By ¹H NMR (internal standard = tetrachloroethane).

^c Determined by ¹H NMR analysis.

Table 3

Oxidative cross-coupling of indoles with simple arenes^a


Entry	Indole	Catalyst	Yield ^b	C2:C3 Selectivity ^c
1		A	52%	1:4.4
		B	66%	4.8:1
2		A	66%	1:5.8
		B	76%	2:1
3		A	71%	1:1.3
		B	68%	5:1
4		A	71%	1.4:1
		B	66%	3.7:1
5		A	54%	1:3.9
		B	71%	2.3:1
6		A	70%	1:1.3
		B	65%	2.6:1

^aCondition A: 5% Pd(TFA)₂ (30 μmol), 5% **2** (30 μmol), indole (0.60 mmol), EtCO₂H (3.6 mmol), benzene (39.6 mmol), 1 atm O₂, 120 °C, 24h. Condition B: 5% Pd(OPiv)₂ (30 μmol), 5% **1** (30 μmol), indole (0.60 mmol), EtCO₂H (3.6 mmol), benzene (39.6 mmol), 1 atm O₂, 120 °C, 24h.

^bIsolated as a mixture of C2 and C3 regioisomers

^cDetermined by ¹H NMR analysis of the reaction mixture.