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Palladium(0)-Catalyzed Dearomative Arylation of Indoles: Convenient Access to Spiroindolenine Derivatives

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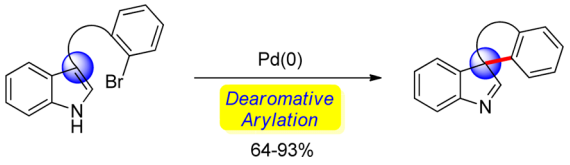
ABSTRACT



Dearomatization of an indole via palladium(0)-catalyzed cross-coupling reaction has been realized. With readily available triphenylphosphine as ligand, various spiroindolenine derivatives have been obtained in good to excellent yields, and enantioselective control is also feasible with chiral ligands.

Dearomatization[1] of arenes and heteroarenes has been widely utilized in the synthesis of complex naturally occurring bioactive compounds and pharmaceuticals.[2] In addition to methods such as metal-mediated alkylation through metal−arene complexation,[3] hypervalent iodine-mediated oxidation,[4] and reductive alkylation under Birch conditions,[5] where a stoichiometric amount of metal reagents or oxidants in general is required, transition-metal-catalyzed dearomatization[6] of aromatic compounds has made significant progress in recent years. Particularly, the Pd-catalyzed cross-coupling reaction,[7] one of the most important reaction types in organic synthesis, was recently also demonstrated successfully in a dearomatization reaction. With an intramolecular design, Buchwald and co-workers recently realized dearomative arylation of aniline derivatives and phenols.[8] On the other hand, indole and its derivatives represent one aspect of the most important

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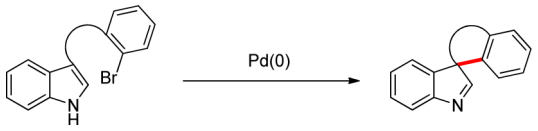
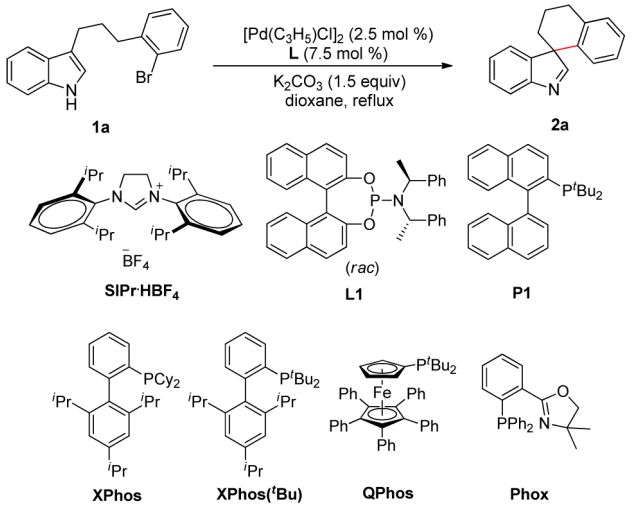
heterocyclic compounds in nature and their transformation has attracted much attention. The 3-substituted indoles have also been reported to be compatible with dearomatization procedures such as iminium catalysis,[1e,f,i–k] cycloaddition,[1h,6m] and the allylic alkylation reaction.[6b–d,i] However, the dearomative arylation of 3-substituted indole via the Pd-catalyzed cross-coupling reaction has been rarely explored[9,10] despite the significant importance of the target spirocycles. Given our interest in developing dearomatization reactions of indole,[6i,l] we recently found that indol-3-yl aryl bromide could be subjected to Pd-catalyzed dearomative arylation reaction (Scheme 1). This intramolecular cross-coupling type dearomatization of indol-3-yl aryl bromides provides spiroindolenine derivatives,[11,12] and the utilization of readily available phosphine ligands potentially allows an asymmetric version of this reaction. Herein we report our preliminary results on this subject.

Scheme 1. Dearomative Arylation of 3-Substituted Indoles



We began our work by testing 3-(3-(2-bromophenyl)-propyl)-1*H*-indole **1a** as the model substrate with readily available palladium precursors and ligands. The results are summarized in Table 1. With the catalyst generated from $[Pd(C_3H_5)Cl]_2$ (2.5 mol %) and PPh_3 (7.5 mol %), the dearomatization reaction of **1a** in the presence of K_2CO_3 (1.5 equiv) in refluxed dioxane (0.2 M) could proceed smoothly, affording desired product **2a** in 85% yield (entry 1). Further screening of various ligands such as $P(^nBu)_3$, SIPr·HBF_4, phosphoramidite **L1**, XPhos, XPhos(^{t}Bu), QPhos, and **P1** revealed that phosphoramidite **L1**[13] gave a slightly higher yield (88%, entry 4). It was worth mentioning that bidentate ligands such as Phox, dppp, and dppf did not lead to the formation of desired product but complete recovery of the starting material (entries 9–11).

Table 1. Screening of Ligands[a]



entry	L	yield (%)[b]	entry	L	yield (%)[b]
1	PPh_3	85	7	QPhos	63
2[c]	$P(^nBu)_3$	N. D.	8	**P1**	complex
3	SIPr·HBF_4	55	9[c]	Phox	N. D.
4	**L1**	88	10[c]	dppp	N. D.
5	XPhos	61	11[c]	dppf	N. D.
6[c]	XPhos(^{t}Bu)	N. D.			

[a] Reaction conditions: $[Pd(C_3H_5)Cl]_2$ (2.5 mol %), **L** (7.5 mol %), K_2CO_3 (1.5 equiv), and **1a** (0.2 mmol) in dioxane (1.0 mL, 0.2 M), reflux. [b] Isolated yields. [c] Conversions determined by ^{1}H NMR.

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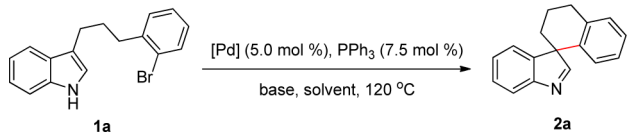
Table 2. Optimization of the Reaction Conditions[a]



entry	[Pd]	base	solvent	yield (%)[b]
1	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	dioxane	85
2	$Pd(OAc)_2$	K_2CO_3	dioxane	52
3[c]	$Pd_2(dba)_3$	K_2CO_3	dioxane	<5
4[d]	$Pd(PPh_3)_4$	K_2CO_3	dioxane	65
5	$[Pd(C_3H_5)Cl]_2$	Cs_2CO_3	dioxane	62
6[c]	$[Pd(C_3H_5)Cl]_2$	K_3PO_4	dioxane	57
7[c]	$[Pd(C_3H_5)Cl]_2$	Li_2CO_3	dioxane	<5
8[c]	$[Pd(C_3H_5)Cl]_2$	NaOAc	dioxane	<5
9[c]	$[Pd(C_3H_5)Cl]_2$	KO^{t}Bu	dioxane	N. D.
10	$[Pd(C_3H_5)Cl]_2$	$NaHCO_3$	dioxane	8
11	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	*o*-xylene	54
12	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	NMP	67
13	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	diglyme	55
14	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	toluene	88
15	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	DMF	77
16	$[Pd(C_3H_5)Cl]_2$	K_2CO_3	DMAc	82

[a] Reaction conditions: Pd source (5.0 mol %), PPh_3 (7.5 mol %), base (1.5 equiv), and **1a** (0.2 mmol) in solvent (1.0 mL, 0.2 M), heated at 120 °C, reflux for dioxane. [b] Isolated yields. [c] Conversions determined by ^{1}H NMR. [d] In the absence of PPh_3.

PPh_3 was chosen as the ligand for further optimization given its ready availability and low cost. As summarized in Table 2, after examining different palladium precursors (entries 2−4) and bases (entries 5−10), the original conditions, $[Pd(C_3H_5)Cl]_2$ (2.5 mol %), PPh_3 (7.5 mol %), and K_2CO_3 (1.5 equiv), were found to be optimal. We then tested the effects of various solvents including *o*-xylene, NMP, diglyme, toluene, DMF, and DMAc (entries 11−16). All the tested solvents could be tolerated, and the reaction in toluene gave the highest yield (88%, entry 14).

Under the optimal reaction conditions (2.5 mol % of $[Pd(C_3H_5)Cl]_2$, 7.5 mol % of PPh_3, 1.5 equiv of K_2CO_3, toluene (0.2 M) at reflux; Table 2, entry 14), different substrates varying substituents and tethers were investigated to evaluate the generality of the reaction. The results are summarized in Table 3. The substrates bearing either an electron-donating group (5-MeO, 4-Me, 7-Me, **2b**−**2d**) or an electron-withdrawing group (5-Cl, 6-F, **2e**, **2f**) on the indole ring were all well-tolerated under the optimized reaction conditions. In general, good to excellent yields could be obtained for the desired dearomatization products. The 2-substituted indolyl products **2g** and **2h** were also compatible to afford dearomatization products in moderate yields. In the case of product **2g**, XPhos[14] was found to be a better ligand than PPh_3.

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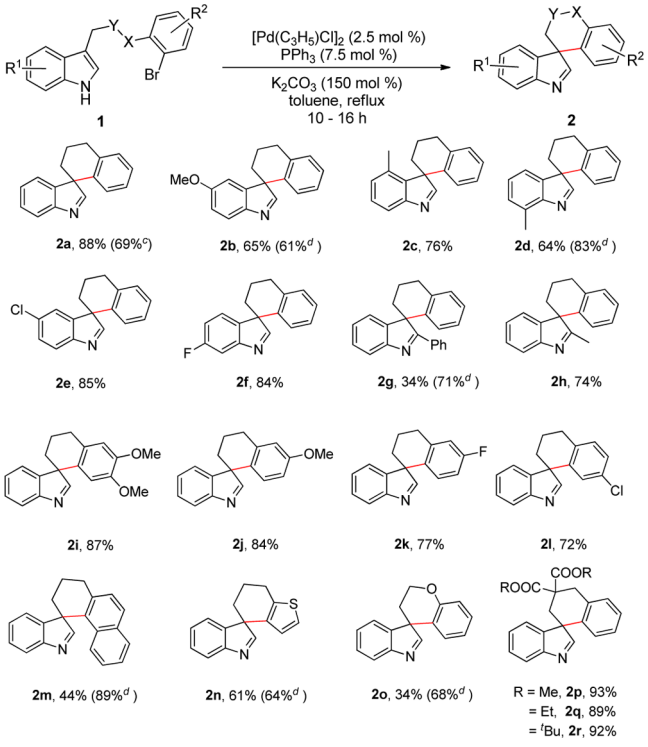
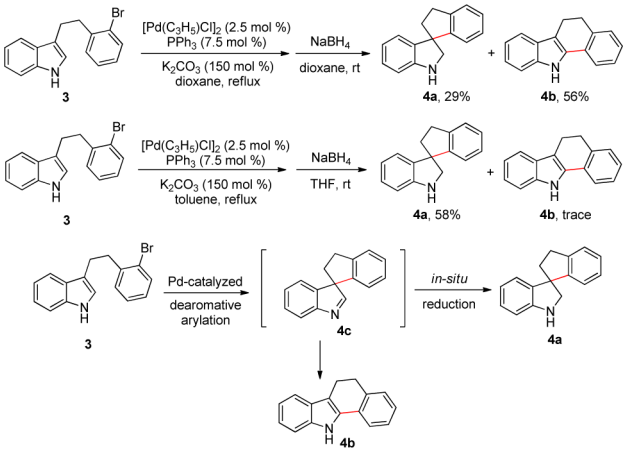
Table 3. Substrate Scope of Dearomative Arylation[a,b]



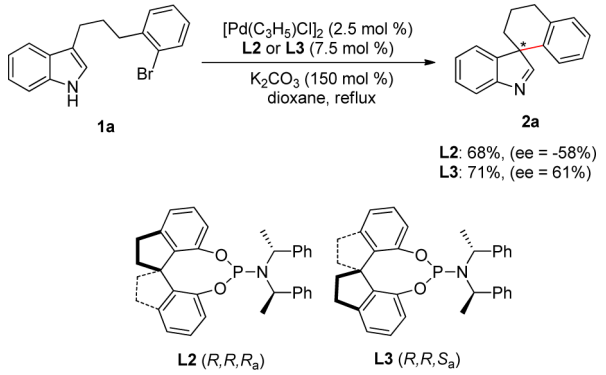
[a] Reaction conditions: $[Pd(C_3H_5)Cl]_2$ (2.5 mol %), PPh_3 (7.5 mol %), K_2CO_3 (1.5 equiv), and **1a** (0.2 mmol) in toluene (1.0 mL, 0.2 M), reflux. [b] Isolated yields. [c] $[Pd(C_3H_5)Cl]_2$ (1.0 mol %), PPh_3 (3.0 mol %) were employed. [d] XPhos was used instead of PPh_3.

Scheme 2. Formation of Five-Membered Ring

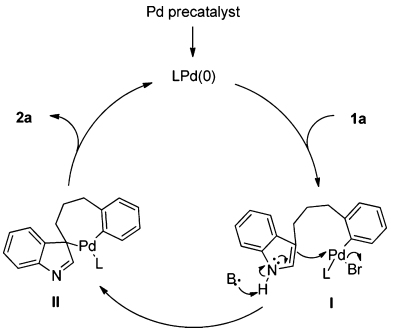


Substituents on the benzene ring including the electron-donating group (**2i**, **2j**) and the electron-withdrawing one (**2k**, **2l**) were all tolerated and led to dearomatization products in 72−87% yields. When the naphthyl substrate was employed, XPhos performed better to afford the corresponding product **2m** in 89% yield. Notably, the thienyl substrate was found to be applicable in this protocol, giving **2n** in 61% yield. Moreover, tethers could also be

Scheme 3. Asymmetric Dearomatization Reaction



Scheme 4. Proposed Reaction Mechanism



varied in the substrates. The *O*-linked product **2o** was obtained in 68% yield with XPhos. The malonate diester linked substrates exhibited higher reactivity, affording products (**2p**−**2r**) in excellent yields (89−93%).

In addition to the six-membered ring formation mentioned above, the five-membered ring formation was also attempted. Substrate **3** by shortening one carbon linkage was tested, as shown in Scheme 2. The five-membered ring dearomatization product was found unstable during the silica gel column chromatography purification. To address this problem, in situ reduction of the dearomatization product with sodium borohydride was carried out, and the desired product **4a** could be obtained in 29% yield. Further optimization of the reaction conditions by changing the solvents (toluene for dearomatization and THF for reduction) could improve the yield of **4a** to 58% by suppressing the formation of compound **4b**. The isolation of products **4a** and **4b** indicated the formation of intermediate **4c** in a dearomatization process and the transformation of **4c** to **4b** via a migration process.[12,15]

The asymmetric version of the current dearomative arylation reaction was also examined. Indeed, screening of commercially available chiral ligands disclosed that moderate ees could be obtained in the presence of chiral spiro phosphoramidate[16] **L2** (58% ee) and **L3** (61% ee) (Scheme 3).

A plausible mechanism for Pd-catalyzed dearomative arylation is depicted in Scheme 4. With in situ generated Pd(0) catalyst, **1a** proceeds oxidative addition to form Pd(II) intermediate **I**. Assisted by base, indole acts as nucleophile through C-3 position to attack palladium center, leading to seven-membered ring intermediate **II**. Then intermediate **II** undergoes reductive elimination to afford product **2a**, meanwhile regenerating Pd(0) species to complete the catalytic cycle.

In summary, we have developed an intramolecular Pd-catalyzed dearomative arylation of 3-substituted indoles, which provides a novel synthetic route of spiroindolenines by generation of a quaternary center at the C-3 position. The preliminary studies also show that the catalytic asymmetric dearomative arylation is feasible. Further extension of the reaction scope and improvement of enantioselectivity are currently ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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