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Palladium-catalyzed intramolecular dearomatization of indoles *via* Heck/Stille cross-coupling with organostannanes

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A palladium-catalyzed tandem intramolecular Heck cyclization/intermolecular Stille coupling for the dearomatization of *N*-(2-bromobenzoyl)indoles is described. This organotin-based protocol provides fused indoline derivatives bearing contiguous quaternary carbon stereocenters at the C2 and C3 positions in moderate to excellent yields and is compatible with structurally diverse organotin reagents, including aryl-, naphthyl-, vinyl ether-, alkenyl-, and alkyl-substituted stannanes. Moreover, this protocol is characterized by mild conditions and gram-scale scalability.

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In recent years, transition-metal-catalyzed dearomatization reactions have emerged as a powerful tool for the efficient construction of a diverse array of three-dimensional complex molecules bearing multiple chiral centers. This strategy has markedly enhanced synthetic efficiency and thus provided a pivotal approach for the synthesis of pharmaceuticals, natural products, and the development of functional materials.¹ Among such compounds, polycyclic fused indolines containing quaternary carbon stereocenters possess rigid three-dimensional architectures and unique electronic properties originating from their fused-ring skeletons. These scaffolds not only serve as the core structural motifs of numerous natural alkaloids and pharmaceutical molecules but also act as important precursors for the fabrication of chiral ligands and functional materials.² Representative examples include (–)-isatisine A,³ (±)-mersicarpine,⁴ gliocladin C,⁵ brevipanamide E⁶ and strychnine (Fig. 1).⁷ Recently, the mainstream strategy for synthesizing tetracyclic fused indolines relies on the intramolecular dearomative Heck reaction of *N*-(2-halobenzoyl) indoles. This transformation generates a key benzyl-palladium intermediate, which can either be trapped by a diverse array of nucleophiles including hydrides, cyanides, organoboron reagents, alkynes, and azoles or undergo transformation *via* β-hydride elimination.⁸

Nevertheless, synthetic methodologies for the preparation of C3-aryl-substituted tetracyclic fused indolines remain scarce, with existing approaches primarily focused on the Suzuki coupling of *N*-substituted indoles with arylboronic acids or arylboroxines.⁹ In 2016, Lautens and co-workers reported

a palladium-catalyzed dearomative 1,2-diarylation of *N*-(2-bromobenzoyl)indoles using triphenylboroxine as the coupling partner, which successfully afforded C3-aryl-substituted polycyclic fused indolines (Scheme 1a).^{9c} In 2021, Zhao's group developed a palladium-catalyzed asymmetric dearomative cyclization of indoles with phenylboronic acids, enabling the stereoselective construction of 3-arylindoline derivatives.^{9a} In the same year, Liang's group adopted a similar strategy for the synthesis of tetracyclic indoline frameworks (Scheme 1b).^{9b} Inspired by these pioneering studies, herein we report a one-pot protocol for the construction of C3-aryl-substituted polycyclic fused indolines. This methodology is based on the palladium-catalyzed dearomatization of *N*-substituted indoles with stable and readily accessible organotin reagents as coupling partners, proceeding *via* a sequential Heck coupling/Stille coupling cascade process.

Initially, *N*-(2-bromobenzoyl)-2-methylindole (**1a**) and tributyl(phenyl)stannane (**2a**) were selected as model substrates

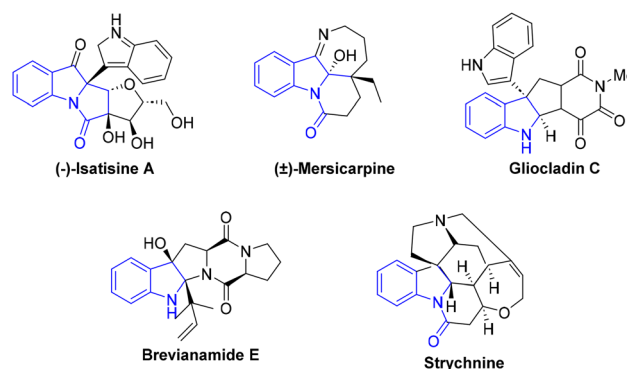
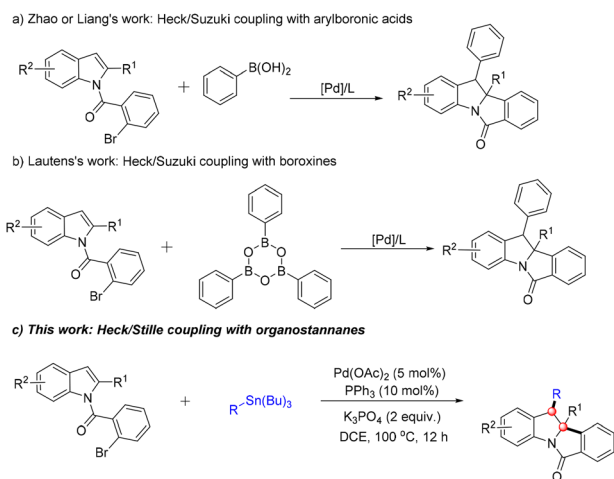


Fig. 1 Some representative natural products and bioactive molecules.

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Scheme 1 Approaches to 3-aryl-substituted indoline derivatives via palladium-catalyzed dearomatization.

Table 1 Optimization of reaction conditions^a

Entry	[Pd]	Ligand	Base	Solvent	Yield ^b %
1	Pd(OAc) ₂	PCy ₃ ·HBF ₄	K ₂ CO ₃	DCE	55
2	Pd(OAc) ₂	PCy ₃ ·HBF ₄	K ₂ CO ₃	THF	25
3	Pd(OAc) ₂	PCy ₃ ·HBF ₄	K ₂ CO ₃	DCM	43
4	Pd(OAc) ₂	PCy ₃ ·HBF ₄	K ₂ CO ₃	Dioxane	36
5	Pd(OAc) ₂	PCy ₃ ·HBF ₄	K ₂ CO ₃	Toluene	30
6	Pd(OAc) ₂	P ^t Bu ₃ ·HBF ₄	K ₂ CO ₃	DCE	45
7	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	DCE	66
8	Pd(OAc) ₂	DPPB	K ₂ CO ₃	DCE	40
9	Pd(OAc) ₂	XPhos	K ₂ CO ₃	DCE	28
10	Pd(OAc) ₂	PPh ₃	Na ₂ CO ₃	DCE	60
11	Pd(OAc) ₂	PPh ₃	NaHCO ₃	DCE	59
12	Pd(OAc)₂	PPh₃	K₃PO₄	DCE	87
13	Pd(OAc) ₂	PPh ₃	NaOAc	DCE	45
14	Pd(OAc) ₂	PPh ₃	Na ₂ HPO ₄	DCE	68
15	PdCl ₂ (CH ₃ CN) ₂	PPh ₃	K ₃ PO ₄	DCE	60
16	Pd(dba) ₂	PPh ₃	K ₃ PO ₄	DCE	59

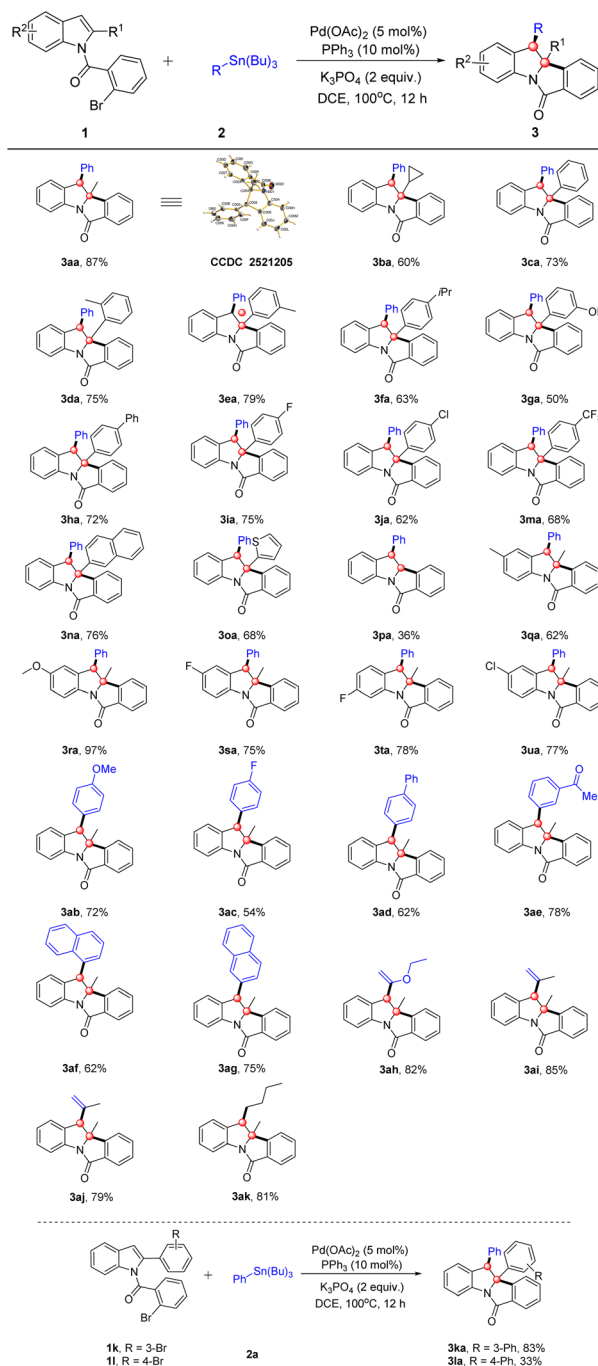
^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Pd] (5 mol%), ligand (10 mol%), base (2.0 equiv.) and solvent (4.0 mL), at 100 °C under N₂ atmosphere for 12 h. ^b Isolated yield.

for the sequential Heck/Stille cross-coupling reaction, and the transformation was investigated under a palladium/ligand catalytic system (Table 1). The dearomatization reaction was first conducted with Pd(OAc)₂/PCy₃·HBF₄ as the catalytic system, K₂CO₃ as the base, in 1,2-dichloroethane (DCE) at 100 °C under nitrogen protection for 12 h, affording the target product **3aa** in 55% yield (Table 1, entry 1). The structure of **3aa** was unambiguously confirmed by single-crystal X-ray

diffraction, providing a solid foundation for subsequent optimization and scope studies. To improve the reaction yield, a systematic series of optimization experiments was subsequently performed. First, various organic solvents were screened, including THF, DCM, 1,4-dioxane and toluene, yet none delivered a superior yield to DCE (Table 1, entries 2–5). Next, a range of phosphine ligands was evaluated to enhance catalytic activity. When PtBu₃·HBF₄, PPh₃, DPPB and XPhos were tested individually, the use of PPh₃ as the ligand led to a slight increase in yield, affording **3aa** in 66% yield (Table 1, entries 6–9). We then focused on the screening of inorganic bases, given that the base plays a pivotal role in modulating reaction kinetics and product formation. The results demonstrated that K₃PO₄ outperformed K₂CO₃ significantly, furnishing **3aa** in an excellent yield of 87% (Table 1, entry 12). In contrast, other bases including Na₂CO₃, NaHCO₃, NaOAc, and Na₂HPO₄ exhibited poorer efficacy in promoting this transformation (Table 1, entries 10, 11 and 13 and 14). Finally, a variety of palladium precatalysts, including PdCl₂(CH₃CN)₂ and Pd(dba)₂, were screened to identify the optimal catalytic precursor. Among these, Pd(OAc)₂ remained the optimal choice, as the other palladium sources resulted in a notable decrease in yield (Table 1, entries 15 and 16). On the basis of the above optimization studies, the optimal reaction conditions were established as follows: 5 mol% Pd(OAc)₂ as the precatalyst, 10 mol% PPh₃ as the ligand, 2.0 equiv. K₃PO₄ as the base, and DCE as the solvent, with stirring at 100 °C under an N₂ atmosphere for 12 h (Table 1, entry 12).

With the optimized conditions established, we further explored the substrate scope of this dearomative cascade transformation. We first evaluated *N*-(2-bromobenzoyl)-2-methylindole (**1a**) and its ring-substituted derivatives, results summarized in Table 2. Indole substrates with various C2 substituents (alkyl/aryl groups) were also compatible, delivering **3aa–3pa** in moderate to good yields. It is noteworthy that substrates bearing an aryl group at the C2 position of the indole ring generally afforded lower yields (50–79%) compared to the methyl-substituted analogue **1a** (87%). This is due to the larger size of the aryl group and altered electronic effects, which impede the key Heck insertion step by increasing steric congestion around the palladium center. Unsubstituted C2 afforded product **3pa** only in 36% yield, much lower than substituted analogues. This is presumably due to the unsubstituted indole's propensity for Heck homocoupling side reactions, reducing the desired product yield. C2 alkyl-substituted indoles (*e.g.*, cyclopropyl) afforded **3ba** in 60% yield. Replacement of C2–H with a phenyl group (either EWG- or EDG-substituted) enabled smooth reaction (**3ca–3ma**). Steric hindrance was negligible, with moderate yields maintained for *ortho*-, *meta*-, and *para*-substituted phenyl groups. C2 substituents such as 2-naphthyl and 2-thienyl (heteroaromatic) also gave good yields (**3na–3oa**), confirming the catalytic system's broad substrate tolerance. The reaction proceeded smoothly when C5/C6 positions of the indole ring bore diverse functional groups, affording products **3qa–3ua** in 62–97% yields. A distinct electronic trend was observed: the electron-donating group (EDG)-substituted substrate **3ra** gave an excellent 97% yield,



Table 2 Substrate scope of substituted isoindolo[2,1-a]indol-6-one^a

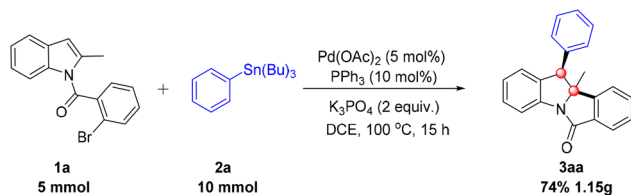
^a Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), [Pd] (5 mol%), ligand (10 mol%), base (2.0 equiv.) and solvent (4.0 mL), at 100 °C under N₂ atmosphere for 12 h.

significantly higher than those with electron-withdrawing groups (EWGs) (**3sa–3ua**).

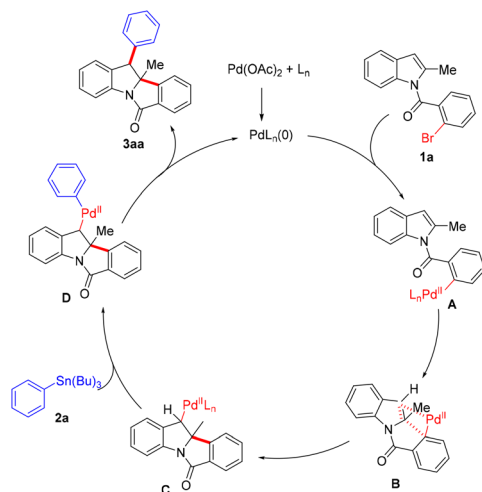
We further extended the study to the scope of organotin reagents with indoles (Table 2). Phenyl-substituted organotin substrates bearing EDGs (methoxy), EWGs (fluoro, formyl) or a phenyl group all reacted smoothly, affording **3ab–3ae** in 54–78% yields. Gratifyingly, replacing the phenyl group with 1-

naphthyl or 2-naphthyl also enabled efficient transformation, giving the products **3af–3ag** in 62% and 75% yields, respectively. Notably, vinyl ether-, alkenyl-, and alkyl-substituted organotin reagents were likewise competent coupling partners, furnishing **3ah–3ak** in 79–85% yields. These results further expand the catalytic system's applicability to structurally diverse organotin reagents. The relative configuration of the C2 and C3 quaternary





Scheme 2 Gram-scale reaction.



Scheme 3 Proposed reaction mechanism.

stereocenters was established as *cis* by X-ray crystallography of **3aa**, and all other products were assigned as single diastereomers with the same relative configuration on the basis of the rigid fused-ring system.

To demonstrate the scalability of this palladium-catalyzed dearomatization reaction, a gram-scale experiment was conducted (Scheme 2).¹⁰ Product **3aa** was scaled up in 10.0 mL DCE at 100 °C for 15 h, using the standard catalytic system (5 mol% Pd(OAc)₂, 10 mol% PPh₃, 2.0 equiv. K₃PO₄). Gratifyingly, the desired product **3aa** was isolated in a synthetically useful 74% yield, verifying the transformation's practical applicability.

Based on our experimental results and published literature, a plausible catalytic cycle for the palladium-catalyzed dearomative cyclization reaction is proposed in Scheme 3.¹¹ Pd(0) species are *in situ* generated from Pd(OAc)₂ and PPh₃ ligands, which undergo oxidative addition with the C–Br bond of aryl bromide **1a** to form arylpalladium complex **A**. Subsequent coordination of the indole C2=C3 bond to the palladium center, followed by intramolecular migratory insertion, furnishes dearomatized alkylpalladium(II) intermediate **C** via transition state **B**. Intermediate **C** then undergoes transmetalation with tributylphenylstannane (**2a**) to form an alkyl(aryl)palladium(II) intermediate **D**. Finally, reductive elimination of **D** yields target product **3aa** and releases Pd(0) to perpetuate the catalytic cycle.

In summary, we have developed a palladium-catalyzed tandem intramolecular Heck cyclization/intermolecular Stille coupling for the dearomatization of *N*-(2-bromobenzoyl)

indoles. This method provides fused indoline frameworks bearing contiguous quaternary carbon centers at the C2 and C3 positions, with a substrate scope encompassing a range of indoles and structurally diverse organotin reagents. Gram-scale synthesis of **3aa** further demonstrates the synthetic utility of this complementary Heck/Stille cascade.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures spectroscopic data. See DOI: <https://doi.org/10.1039/d6ra02185a>.

Acknowledgements

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